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Endocrine Status of the Periparturient Mare and Induction of Estrus After Foal Heat With Prostaglandin F(2 Alpha).

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ENDOCRINE STATUS OF THE PERIPARTURIENT MARE AND INDUCTION OF ESTRUS AFTER FOAL HEAT WITH PROSTAGLANDIN $F_{2\alpha}$

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ABSTRACT

Two studies were conducted during the breeding seasons of 1974 and 1975 to monitor steroid levels in the peri-parturient mare and newborn foal (Experiment I) and to determine the feasibility of using prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) to control the estrous cycle of the postpartum lactating mare (Experiment II). In trial 1 of the first study, plasma steroid levels were determined in nine Quarter Horse mares during the 7 days prior to parturition through 2 days postpartum. Blood samples were collected at 6 hr. intervals by jugular puncture. Progestin and corticoid concentrations were determined by competitive protein binding and estrogen levels by radioimmunoassay. Steroid levels were also determined on a plasma sample from foals at birth and at 24 hr. postpartum. Plasma progestin concentrations in the mares decreased ($P < .01$) from $13.4 \pm .6$ ng/ml on day 3 prepartum to $3.2 \pm .5$ ng/ml on the day of parturition. Estrogen levels also declined ($P < .01$) from day 3 prior to foaling (306.2 ± 11.4 pg/ml) to the day of parturition (193.4 ± 9.0 pg/ml). However corticoid concentrations increased ($P < .01$) from 85.8 ± 10.8 ng/ml on day 3 before parturition to a peak of 140.0 ± 9.8 ng/ml on the day of foaling. There was no significant diurnal variation of progestin, estrogen or corticoid levels in pre- or post-partum mares, but corticoid levels tended to be higher in morning than in evening samples. Mean progestin and

corticoid concentrations in the newborn foals decreased ($P < .05$) during the 24 hr. postpartum, while estrogen levels remained relatively constant.

The study was repeated in 1975 using a total of nine mares. Trial 2 was similar to the previous trial except that blood samples were collected at 12 hr. intervals. Progestin levels dropped ($P < .01$) from $5.3 \pm .6$ ng/ml on day 3 prepartum to near nondetectable levels on the day of parturition. Plasma estrogens declined ($P < .01$) from 360.9 ± 14.2 ng/ml on day 3 prior to foaling to 198.8 ± 12.7 pg/ml on the day of parturition. In contrast to the peak in corticoid levels observed on the day of parturition in the first trial, levels in trial 2 decreased on the day of foaling (77.9 ± 7.4 ng/ml). Progestin and estrogen levels showed no diurnal variation, however, mean corticoid levels were higher ($P < .01$) in morning than in evening collected samples. Again, progestin ($P < .01$) and corticoid levels in the newborn foals decreased during the 48 hr. postpartum while estrogen levels remained relatively unchanged.

In the second study two trials were conducted to determine if prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) could be used to induce estrus in mares shortly after foal heat and thereby reduce the time from foaling to rebreeding while circumventing the undesirable effects of breeding on foal estrus. In the initial trial four mares were given a 10 mg (SC) injection of $PGF_{2\alpha}$ - free acid, five mares were injected

with 15 mg (SC) of $PGF_{2\alpha}$ - tham salt and five females were given an injection of sterile saline on days 6 and 7 after the end of foal heat. Treatment with $PGF_{2\alpha}$ - free acid and $PGF_{2\alpha}$ - tham salt shortened ($P < .01$) the interestrual interval when compared to controls. In addition the interval between foaling and the onset of the second estrus was decreased ($P < .01$) as a result of treatment with $PGF_{2\alpha}$ - free acid (23.0 $\pm$ 2.3 days) or $PGF_{2\alpha}$ - tham salt (24.6 $\pm$ 2.1 days) as compared to control mares (34.2 $\pm$ 2.1 days). Thus the time interval from foaling to rebreeding was reduced in the treated mares. Treatment with $PGF_{2\alpha}$ did not appear to adversely affect fertility since all of the $PGF_{2\alpha}$ - free acid and control mares and four of five $PGF_{2\alpha}$ - tham salt treated females conceived on the second estrus after foaling. Treatment with $PGF_{2\alpha}$ - tham salt resulted in a rapid drop in progestin levels from a mean pretreatment level of 2.9 $\pm$ 1.7 ng/ml to .4 $\pm$ .2 ng/ml 15 min. following the second injection.

The experiment was repeated in 1975 using Prostin $F_{2\alpha}$®. On day 6 and 7 after foal estrus nine treatment mares were given 15 mg (IM) injections of Prostin $F_{2\alpha}$® and seven control mares were injected (IM) with saline. Again, the interestrual interval was shorter ($P < .01$) for treated mares than for controls. Treatment of mares with Prostin $F_{2\alpha}$® shortened ($P < .01$) the interval between

foaling and the second postpartum estrus by 8.8 days resulting in a shortening of the time from foaling to rebreeding similar to that reported for trial 1. In contrast to the results of the initial trial the conception rate in trial 2 was somewhat lower for treated (44%) than for control (85%) mares. The luteolytic effect of $PGF_{2\alpha}$ was confirmed by the rapid drop in progestins from a mean pretreatment level of $3.3 \pm .7$ ng/ml to $1.2 \pm .4$ ng/ml on the second day of treatment.

CHAPTER I

INTRODUCTION

Reproductive efficiency of horses is lower than that of other domestic animals with respect to both conception rate and the percentage of live foals born. According to Nishikawa and Hafez (1968) conception rate in mares ranges from 60 to 65% with the foaling percentage only about 50 percent. Contributing to this poor reproductive efficiency in horses is a relatively high abortion rate ranging from 10 to 19% (Nishikawa and Hafez, 1968; Murray Bain, 1969) and failure to properly synchronize mating with ovulation. The recent development of sensitive and reliable assay methods for measuring plasma hormone levels and the discovery of compounds to control the estrous cycle of other farm species has stimulated interest in these areas as possible ways of improving the reproductive performance of mares.

As a result of the high abortion rate in mares it is of considerable importance to understand the endocrine events associated with the initiation of parturition. However, relatively few studies have been done to determine steroid hormone levels during gestation and parturition in the mare. A knowledge of the levels of these hormones in the blood of mares at parturition and in the newborn foals would be helpful in examining the

mechanisms controlling parturition. Moreover, a comparison of hormone levels in normal foaling mares with those which frequently abort may lead to a greater understanding of the etiology of equine abortion. This information would also be beneficial in the investigation of methods for the induction of parturition in mares which could result in savings of both labor and foal death losses.

The most promising estrous control compound under study at the present time is prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Numerous investigators have demonstrated that $PGF_{2\alpha}$ causes luteolysis in the cycling mare. The compound may also be helpful in the treatment of anestrous mares.

Early workers observed that females bred on the second estrus after foaling had higher conception rates with fewer cases of abortion, dystocia and dead born foals than those bred at foal estrus (Jennings, 1950; Trum, 1950). Despite these detrimental effects, the practice of breeding on foal heat persists because most breeders are intent on having foals born as close as possible to the universal birth date of January 1.

In view of the low conception rate and the relatively high percentage of abortions occurring in mares, two experiments were conducted to obtain information to improve the reproductive efficiency of horses. The objective of the first experiment was to concurrently determine the peripheral plasma progestin, estrogen and corticoid levels in

the mare at parturition and in the newborn foal. The second experiment was initiated to determine if prostaglandin $F_{2\alpha}$ could be used to induce estrus in mares shortly after foal heat and thereby reduce the postpartum interval while circumventing the undesirable effects of breeding on foal heat.

CHAPTER II

REVIEW OF LITERATURE

This review will describe the hormonal status of gestating farm species including information pertinent to the endocrine status of the pregnant mare. Also, literature will be reviewed concerning estrous control in farm animals with emphasis on the effects of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and $PGF_{2^{\alpha}}$ analogues on the estrous cycle of the mare. In addition, information will be presented relative to the practice of breeding mares at foal heat.

Progestin Levels During Gestation and Parturition

Characterization of hormone levels during gestation is of considerable importance in determining the causes of high abortion rates in mares. Although steriod hormone levels during pregnancy and parturition have been studied quite extensively in the cow, ewe, and sow, considerably less is known concerning the endocrine status of the mare during this stage of the reproductive cycle.

Cow. Early workers (Short, 1958; Bowerman and Melampy, 1962; Gomes et al., 1962; McCracken, 1964) reported that progesterone levels in the peripheral plasma of cows increased rapidly during the first few weeks of gestation and reached a peak on day 30. Levels then decreased and remained fairly stable until day 220 when progesterone

concentrations increased. Subsequently progesterone levels gradually declined until parturition occurred. More recent studies (Pope et al., 1969; Donaldson et al., 1970; Stabenfeldt et al., 1970; Henricks et al., 1972; Smith et al., 1973) demonstrated that progesterone concentrations during early bovine pregnancy were similar to luteal phase values. Concentrations declined during midpregnancy and increased to a maximum at 240 days of gestation. Progesterone levels started to decline 2 to 3 weeks before calving and fell abruptly 24 hr. before parturition.

Ewe. Progestins were first detected in the peripheral blood of pregnant ewes by Neher and Zarrow (1954) who found that levels rose in 10 ewes from 1 to 2 ug/ml at mating to a peak of 8 to 12 ug/ml at parturition. In all 10 ewes lambing occurred prior to the drop in serum progestins. Similar results were reported by Short and Moore (1959) who noted that progesterone levels remained elevated in the ewe until after lambing was completed. Edgar and Ronaldson (1958) measured progesterone in ovarian vein blood collected from 108 ewes at various times throughout pregnancy and noted that the corpus luteum secreted the hormone until about 2 weeks before lambing. In a more recent study, Stabenfeldt et al., (1972) demonstrated that peripheral plasma progesterone levels in 25 ewes during the first 50 days of pregnancy were similar to concentrations found during the luteal phase of the estrous cycle. A gradual

increase in progesterone concentration began at week 8 in ewes with twin lambs and at approximately week 11 in ewes carrying single lambs. A gradual decline in progesterone concentration began at week 19 in both groups and continued to the day of parturition. These results suggest that in the ewe endocrine preparation for delivery begins 2 weeks prior to parturition. These trends are in general agreement with the work of Bassett et al., (1969), Basson et al. (1969) and Fylling (1970). The failure of earlier workers (Neher and Zarrow, 1954; Short and Moore, 1959) to find significant changes in progesterone concentrations at the time of parturition was probably due to lower sensitivity of the assay used.

Sow. Progesterone levels in the prepartum sow appear to follow a trend similar to that observed in the ewe. Kimura and Cornwell (1938) measured the progesterone content of the pregnant sow and observed that levels declined markedly during the week before farrowing. More recent studies with the sow demonstrated that during the first 14 days of pregnancy the plasma progesterone concentrations were similar to those found during the luteal phase of the estrous cycle (20 to 30 ng/ml) but declined gradually (10 to 15 ng/ml) during midpregnancy (Tillson and Erb, 1967; Guthrie et al., 1972; Robertson and King, 1974). During the last month of pregnancy plasma progesterone levels

ranged from 6 to 12 ng/ml and decreased sharply (.5 to 2 ng/ml) just before farrowing (Killian et al., 1973; Molokwu and Wagner, 1973; Edqvist et al., 1974; Robertson and King, 1974; Ash and Heap, 1975).

Mare. Although numerous investigators have studied progesterone levels during gestation and parturition in the cow, ewe and sow, relatively few studies have been conducted with the pregnant mare. Progesterone levels in the blood of the pregnant mare were studied initially by Short (1959). Progesterone in four samples was highest (5 to 14 ng/ml) during the early months of pregnancy when accessory corpora lutea were still present in the maternal ovaries. However, after the fourth or fifth month of gestation the hormone was undetectable in maternal blood, despite the increasing excretion of pregnanediol derivatives in the maternal urine. Also, progesterone was present in high concentrations (38 to 63 ng/ml) in umbilical cord blood collected from three foals during parturition. The author suggested that the placenta is probably still producing progesterone at the time of birth. The failure to detect progesterone in the maternal blood of the mare during late gestation was possibly due to the lack of sensitivity of the assay used.

In more recent studies, Allen and Hadley (1973) and Allen and Hadley (1974) encountered large individual

variation in progesterone levels of 16 mares during early pregnancy. In 13 normal pregnancies the hormone increased initially then gradually decreased from days 20 to 30 of gestation. Progesterone concentrations tnen varied between 2 and 10 ng/ml for the first 5 months of pregnancy. Three pregnancies were accompanied by lower than average progesterone levels and conceptual loss occurred. In contrast, Squires et al. (1974) found that progesterone levels in 17 pregnant mares increased from days 32 to 44 (10.8 ng/ml), attained a maximum on day 90 of 18 ng/ml followed by a decrease from day 150 to 180 of pregnancy.

Progesterone levels were first measured throughout pregnancy in the mare by Smith (1974) who collected blood from 8 females at intervals of 1 to 6 weeks during gestation and for 2 days postpartum. The trend in progesterone concentrations for the first 5 months of pregnancy was similar to that reported by Squires et al. (1974). Progesterone levels fell to a minimum of 6.4 ng/ml at about 180 days of gestation and rose to the highest level (11.5 ng/ml) from 270 days to term. By day 2 postpartum progesterone concentration had fallen to .5 ng/ml, indicating that secretion of the hormone had virtually ceased.

A similar trend in progesterone concentrations was observed by Holtan et al. (1975a) in plasma collected from 13 mares at various times throughout pregnancy. During early pregnancy, progesterone increased from 1.1 ng/ml on

day 0 to a maximum concentration of 15.2 ng/ml on day 64. Thereafter, progesterone gradually declined and remained between 1 and 2 ng/ml from days 180 to 300. During the last 30 days of gestation, progesterone increased to 4.4 ng/ml at day 5 prepartum and dropped precipitiously to less than .5 ng/ml on or near the day of foaling.

In contrast to the results of the two previous studies, Noden et al. (1975) observed that blood progesterone levels remained elevated throughout pregnancy. Progesterone averaged 9.2 ng/ml at 45 days, increased to 16.1 ng/ml at 180 to 195 days and then decreased slightly to 13.4 ng/ml at 285 days of pregnancy. Levels averaged 24 ng/ml 2 days before parturition, decreased to 3.3 ng/ml on the day of foaling and remained about 1 ng/ml until foal estrus began.

Differences in progesterone levels among the foregoing studies may be explained in part by assay cross-reactions of unidentified compounds which were recently reported by Holtan et al. (1975a) to be present in the plasma of mares between 30 and 60 days of gestation. These compounds increased gradually to day 300, with a significant increase 5 days before parturition. The unknown substances were not detected during the postpartum period. In a subsequent study, Holtan et al. (1975b) identified these compounds as 5α- pregnan-3, 20 - dione, 3 β -hydroxy- 5α - pregnan-20-one and 20α - hydroxy- 5α -pregnan-3-one and concluded

that these pregnanes are present in the peripheral circulation of pregnant mares and are produced or metabolized by the feto-placental unit.

Estrogen Levels During Gestation and Parturition

Estrogenic substances, are continously implicated as an important part of the metabolic mechanisms dealing with reproductive performance of animals and like progestins have been studied extensively in the gestating cow, ewe and sow. However, there is a paucity of information on estrogen levels in the pregnant mare.

Cow. Estrogenic activity in the urine of the pregnant cow was discovered by Hisaw and Meyer (1929), Nibler and Turner (1929) and Turner et al. (1930) who reported that the hormone increased throughout pregnancy. Later findings indicated that a peak estrogen excretion occurred in urine immediately before calving, followed by a steady decline postpartum (Mellin et al., 1964). Until recently there were few studies describing estrogen levels in the peripheral blood of the pregnant bovine. In 1972 Henricks et al. reported that peripheral plasma estrogen levels remained low (less and 5 pg/ml) in pregnant cows from day 3 until day 39 postinsemination. In general, levels began to rise during midpregnancy (Erb et al., 1968; Hoffmann et al., 1973). Henricks et al. (1972) reported that during the 14

days prior to parturition estrogen increased from 500 pg/ml to 2660 pg/ml on the day of parturition. For the last 5 days of pregnancy estrogen concentration increased at the rate of 248 pg/day. After parturition, estrogen levels ranged from nondetectable to 40 pg/ml. Similar results for bovine estrogen levels during late pregnancy and at parturition have been reported by Hunter et al. (1970), Hoffmann et al. (1973) and Smith et al. (1973).

Ewe. In contrast to levels reported in the cow, total estrogens in the peripheral blood of the ewe were less than 20 pg/ml for most of pregnancy (Challis, 1971; Challis et al., 1971). Levels rose to 40 to 50 pg/ml within 5 days of lambing and increased very sharply (75 to 411 pg/ml) during the last 48 hr. of gestation (Challis, 1971; Robertson and Smeaton, 1973). Estrogens were not detectable by the first day postpartum (Challis, 1971).

Sow. Unlike early studies in the cow where urinary estrogens were reported to increase throughout pregnancy, Kurst and Struck, 1934 observed that in the sow estrogenic substances were excreted into the urine at two periods of gestation, namely at week 4 and 5 after breeding and during the last 6 weeks prior to parturition as cited by Velle, 1958. These observations support earlier investigations based on data obtained using a biological assay (Grumsell and Robertson, 1953) and fluorescent tests (Roth et al. 1941;

Grumsell and Robertson, 1953). More recent studies, employing sensitive assay methods, have demonstrated that plasma estrogen concentrations in the sow during the first 24 days of pregnancy were within the range of 10 to 28 pg/ml (Guthrie et al., 1972). The urinary secretion of estrogens reached a peak at the end of the first month of pregnancy, declined during midpregnancy and increased again towards the end of gestation (Lunaas, 1962; Raeside, 1963). Seven to 9 days before farrowing, the concentrations of plasma estrogens increased steadily and reached a peak on or near the day of parturition (Molokwu and Wagner, 1973; Edqvist et al., 1974; Roberston and King, 1974; Ash and Heap, 1975). Ash and Heap (1975) observed that plasma estrogens declined gradually after the onset of parturition and reached low values (1 ng/ml) only after the delivery of all piglets and placentae.

Mare. As in earlier estrogen studies with the cow and sow, estrogen levels in the mare during pregnancy were first monitored in the urine. In 1935 Cole and Saunders showed that estrin appeared in the urine of three mares at about day 100 of pregnancy. The highest concentration was found between day 200 and 275. The concentration then declined and a day or two after foaling estrin could no longer be detected in the urine.

In a later study, Savard (1961) used a partition chromatographic method to study the urinary estrogens estrone, equilin and equilenin in five pregnant mares. He concluded that estrone and equilin were the principal components and equilenin a minor constituent of the mare's estrogens. Levels of equilin rose from the fourth and fifth months to equal and in some cases exceed those of estrone in the late months of pregnancy.

Recently, Nett et al. (1973) determined the concentration of estrogens in the peripheral plasma of eight mares during gestation and the postpartum period. Column chromatography was used to separate fraction E_1, (estrone, equilin and equilenin) and fraction E_2 (estradiol) after ether extraction. The concentration of E_1 remained below 20 pg/ml from breeding to day 80 of gestation, increased to 828 pg/ml at 210 days of pregnancy, then declined until foaling; basal levels were observed by day 1 postpartum. The concentration of E_2 remained below 15 pg/ml until day 90, increased to 71 pg/ml at 240 days, then declined until 300 days of pregnancy and remained relatively unchanged until parturition. Estradiol (E_2) returned to basal levels by day 1 postpartum. Abortion occurred in one mare 203 days after insemination. However concentrations of E_1 and E_2 in the plasma of this mare were not abnormal with respect to the mares that foaled. Nett et al. (1973) suggested

that a lack of estrogens was not the cause of abortion in this mare.

Corticoid Levels During Gestation and Parturition

In addition to progestins and estrogens, corticoids have also been implicated as having an influence on the reproductive processes of several species including the cow, ewe, sow and mare (Turner and Bagnara, 1971).

Cow. A study of the plasma levels of the 17-hydroxy-corticosteroids in cows by Shaw et al. (1960) revealed no particular pattern in the levels of this compound in pregnant females sampled from 1 to 9 months before calving. Brush (1958) observed that except for one case where calving was difficult, there was no evidence of increased 17-hydroxycorticosteroid levels associated with the time of labor. However, other researchers (Adams and Wagner, 1970; Heitzman et al., 1970; Hoffmann et al., 1973) have demonstrated a significant rise (8 to 14 ng/ml) in corticoid levels during the last 4 days prior to parturition. Smith et al., (1973) noted that corticoids remained low until the day before calving (6.4 ng/ml) and increased dramatically to 16.7 ng/ml at parturition. Corticoid levels fell to basal levels about 12 hr. postpartum. The results of these studies indicate a high degree of variability in bovine corticoid levels and it has been suggested that the rise

in levels near the time of parturition may be a result rather than an initiator of parturition.

Ewe. In contrast to levels observed in the cow, Bassett and Thorburn (1969) reported that plasma maternal corticosteroid concentrations in the ewe were generally less than 20 ng/ml during the prepartum period and bore little relation to fetal levels. Starting several days before birth, there was an increase in the plasma corticosteroid concentrations of all the sheep fetuses, unrelated to changes in maternal corticosteroid levels. The highest fetal concentrations (120 ng/ml), which were considerably above maternal levels (20 ng/ml), were reached at the time of birth (Bassett and Thorburn, 1969).

Studies by Kennedy et al., (1967) and Drost and Holm (1968) demonstrated the importance of a functional fetal adrenal for normal parturition in the ewe. Complete bilateral removal of the adrenal glands of sheep fetuses in utero 1 month before term resulted in failure of 37 ewes to undergo labor (Drost and Holm, 1968). Also infusion of an adrenalectomized post-term fetus with ACTH for nine days had no effect on pregnancy (Kennedy et al., 1967). However the continous administration of ACTH or cortisol to intact ovine fetuses in utero resulted in parturition within 4 to 7 days (Liggins, 1969). Liggins (1969) also demonstrated that dexamethasone treatment (.06 to 4.0 mg/24 hr.) of the

fetus gave similar results while treatment of pregnant ewes at the rate of 4 mg of the drug per 24 hr. did not result in premature delivery. The administration of glucocorticoids in large doses to pregnant ewes beyond day 133 caused premature delivery in half of the animals within 4 or 5 days whereas treatment earlier in pregnancy was usually ineffective (Adams and Wagner, 1970; Skinner et al., 1970; Fylling, 1971).

Sow. Corticoid levels in the sow appear to be similar to those in the ewe varying between 20 and 35 ng/ml during most of the prepartum period (Killian et al., 1973). Approximately 24 hr. before farrowing, corticoid concentrations began to rise and peaked (51 to 101.8 ng/ml) on the day of parturition (Killian et al., 1973; Molokwu and Wagner, 1973). Corticoids returned to prefarrowing levels by 2 days postpartum (Molokwu and Wagner, 1973). Both Killian et al., (1973) and Molokwu and Wagner (1973) interpreted the elevation in corticoid levels at farrowing to be a result and not a cause of parturition. In contrast, Ash and Heap (1975) reported that plasma corticosteroid concentrations in the pregnant sow varied appreciably from day to day and observed no consistent change at the time of parturition.

Mare. A review of the literature revealed no studies on the concentration of corticoids in the mare throughout pregnancy, at the time of parturition nor in the newborn

foal. However, Hoffis et al. (1970) attempted to determine the influence of pregnancy on corticoid concentrations in the mare. One sample of blood was collected by jugular venipuncture from each of 26 pregnant mares and analyzed by a competitive protein binding technique. The stage of pregnancy of mares at the time of blood collection was not given. Nevertheless the authors concluded from this experiment that pregnancy had no effect on corticoid levels in the mare.

Effect of Synthetic Corticoids on the Gestating Mare

Although there is a paucity of information on circulating corticoid levels in the pregnant equine, studies have been conducted to determine the effect of synthetic corticoids on gestation in the mare. Dexamethasone, a synthetic and more potent analogue of prednisolone, administered daily to mares for 5 days during the first trimester of pregnancy at the dosage rate of 10 to 40 mg per day did not result in abortion (Campbell, 1971). Attempts to induce parturition with two or more injections of dexamethasone (20 mg each) in five shetland pony mares during the last 2 months of pregnancy were also unsuccessful (Drost, 1972). However, when pregnant mares were given 4 daily massive doses of dexamethasone (100 mg on each of days 321 through 324 of gestation), premature parturition occurred (Alm et al., 1974).

Diurnal Variation in Corticoid Levels

Awareness of a diurnal or circadian variation in adrenal cortical production is of practical significance in planning experiments that monitor corticoid concentrations. Diurnal variation in adrenocortical function was first detected by Pincus (1943) who noted that urinary excretion of 17-ketosteroids in young men was greater during the day than at night. Diurnal variation in urinary excretion of cortisol metabolites was demonstrated in 1949 by Romanoff et al., (1949). Maximum excretion usually occurred in the morning, although occasionally it came later in the day. Diurnal variation in adrenocortical function has also been demonstrated in the cow (Wagner, 1970; MacAdam and Ederhart, 1972; Wagner and Oxemreider, 1972), sow (Killian et al., 1973) and horse (Zolovick et al., 1966; Hoffis et al., 1970; Bottoms et al., 1972).

Studies by Wagner (1970) and Wagner and Oxenreider (1972) demonstrated that blood plasma samples taken from cows during the late pm hours (1800 to 2400 hr.) were significantly lower in corticoid concentration than samples obtained at other time periods. Mac Adam and Eberhart (1972) noted a similar diurnal variation in bovine corticoid levels.

Killian et al., (1973) observed a diurnal variation in corticoid levels in the prepartum sow until 24 hr. prior to

parturition, and then again following farrowing. The concentration of corticoids in morning samples (19.7 ng/ml) was significantly higher than evening levels (14.6 ng/ml).

A diurnal variation in glucocorticosteriod levels in the horse was first demonstrated by Zolovick et al., (1966). In five mature geldings the highest level of cortisol was found at 1000 hr. and the lowest concentration at 2200 hours. More recently, Hoffis et al., (1970) and Bottoms et al., (1972) obtained blood samples from mature mares and observed that cortisol values were high in the morning collected samples and low in the evening samples.

This review of the literature on the endocrine status of gestating farm species revealed little information on the circulating levels of progestins, estrogens or corticoids in the periparturient mare. Since this information may be beneficial in determining the etiology of equine abortion studies are needed to determine hormone levels in the mare near the time of parturition and in the newborn foal.

Control of the Estrous Cycle of the Mare

Another factor contributing to the low reproductive efficiency in horses is the failure to properly synchronize mating with ovulation. There have been several attempts to control the estrous cycle of the mare in order to reduce the variation in length of estrus and time of ovulation

and therefore allow breeding at a time when there is the highest likelihood of fertility. Studies to control estrus have involved the use of synthetic and natural hromones, sterile saline, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), and $PGF_{2\alpha}$ analogues.

Induction of Ovulation. The first attempt to control the variability in time of ovulation and length of estrus in mares was reported by Mirskaya and Petropavolsky (1938) who observed that an injection of 1000 mouse units (mu) of prolan (a preparation obtained from the urine of pregnant women) on the first day of estrus resulted in a marked reduction in the interval from onset of heat to ovulation and shortened the duration of estrus. Although no controls were used, the authors stated that the foaling percentage (77.8 and 83.8 for trial 1 and 2, respectively) appeared to be unaffected by treatment. In a similar study, Day (1940) demonstrated that intravenous injections of 1000 to 2000 mu of a pregnancy urine extract when given to pony mares during estrus were capable of inducing ovulation within 20 to 40 hr, provided a fairly mature follicle was present in the ovary. Similar results using pregnant human urine extracts were later reported by Davidson (1947).

More recently, Loy and Hughes (1966) conducted a 4 year study to determine the effects of intravenous injections (2000 IU) of human chorionic gonadotropin (HCG) on the interval from onset of estrus to ovulation in 68 mares.

Treatment with HCG on day 2 of estrus reduced the interval from onset of estrus to ovulation with no adverse effects on fertility. Moreover, breeding efficiency was improved since fewer services per conception were required in treated mares as compared to controls. Sullivan et al. (1973) observed a similar effect of HCG on the time of ovulation. However, when HCG was given during three successive estrus periods, the response after the third administration differed significantly from that after the first injection. The average duration of estrus was longer and ovulation did not occur within a precise time following the third treatment with HCG. The effects of HCG administration on estrus, ovulation and fertility were also confirmed by Voss et al. (1974).

Recently a synthetic compound called gonadotropin releasing hormone (GnRH) induced ovulation in hamsters, rabbits, chickens, sows, ewes, and cows as reviewed by Schally et al. (1972) and Crighton (1975). However, the effect of this synthetic hormone in mares has received less attention. Ginther and Wentworth (1974) reported that treatment of estrous mares with 400 ug of GnRH on day 2 of estrus caused an increase in plasma luteinizing hormone (LH) concentrations but did not significantly alter follicular development or time of ovulation. Downey et al. (1974) observed that an injection of 1 mg GnRH on day 2 of estrus significantly shortened the duration of estrus and the interval from onset of estrus to ovulation. Similar

findings were reported by Kreider et al. (1976). However GnRH treated mares had a lower conception rate at the treatment estrus than control mares. GnRH treatment did not alter subsequent estrus or fertility.

Inhibition of Ovulation. Another approach to control the estrous cycle has been to inhibit ovulation in a group of females until all existing corpora lutea become non-functional, then remove the inhibitor thus theoretically allowing all animals to return to estrus at about the same time. Loy and Swan (1966) tested the effects of administering the natural steriod progesterone as well as the synthetic progestins 6α - methyl - 17α metoxyprogesterone (MAP) and melengesterol acetate (MGA) to mares during the luteal phase of the cycle. Neither the synthetic progestins nor orally administered progesterone were effective in blocking estrus or ovulation. However, daily injections of 100 mg of progesterone blocked both estrus and ovulation but failed to prevent the growth of follicles. Daily injections of progesterone at this level from day 4 through day 12 postpartum blocked foal estrus but did not inhibit ovulation.

Another ovulation inhibitor, methallibure or ICI 33,828 has been effective in the synchronization of estrus in gilts, with fertility and embryonic survival remaining normal subsequent to treatment (Hafez et al., 1966). Experiments with this nonhormonal ovulation inhibitor in mares indicated a pronounced inhibition of gonadotrophin

secretion (Loy, 1966; First, 1973). First (1973) reported that treatment of 67 mares with methallibure, resulted in a reasonable control of estrus and ovulation but when the drug was administered orally at doses of .5 to 2.5 g per day for 18 to 20 days inappetence occurred and treatment by way of bolus was required. A high frequency of mares receiving 1.5 g or more of the compound by bolus became lethargic or staggered during treatment. Most mares treated with methallibure showed estrus after treatment (47 of 50) and 43 of 47 that came into estrus ovulated. Treatment with the drug did not significantly alter the pregnancy rate from that of controls.

Regression of the Corpus Luteum. Control of the estrous cycle can also be accomplished by inducing early regression of the corpus luteum. Vandeplassche (1963) reported that the intrauterine infusion of water was used as early as 1935 to control the estrous cycle of the mare. Later studies (Arthur, 1968; Arthur, 1970; and Ginther and Meckley, 1972) have dealt with the influence of intrauterine infusion of sterile saline in the mare at various times during the estrous cycle. Infusion during estrus, prior to day 4 of diestrus and late in diestrus appeared to have little effect on cycle length. However, saline infusion beginning on day 4 postovulation shortened, the cyclic ovulatory interval in the majority of mares. In a recent study, Neely et al. (1974) demonstrated that infusion

of the uterus of 10 mares with 250 ml of warm sterile saline on day 4, 5, 6 or 7 postovulation shortened the cyclic ovulatory interval. The action of this treatment was through the initiation of corpora lutea regression since plasma progestin concentrations began to decline approximately 1 day following infusion and fell to less than 1.0 ng/ml by 4 days after treatment. These studies suggest that an active corpus luteum of sufficient maturity (4 to 5 days postovulation) is required for intrauterine saline infusion to induce estrus and to shorten the interovulatory interval.

The recent discovery of the luteolytic effect of a compound called prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) has given additional impetus to this approach to controlling the estrous cycle of the mare. Prostaglandins are a family of lipids discovered in extracts of human semen and sheep seminal vesicles in the 1930's (Kurzrok and Lieb, 1930; Goldblatt, 1933, 1935; von Euler, 1934). These compounds are all 20-carbon fatty acids, have the same basic "skeleton", prostanoic acid, and are derived from essential fatty acids by cyclization and oxidation. Prostaglandins have a wide spectrum of activities and individual compounds differ in their actions. They act in smooth muscle stimulation as well as in relaxation (Bergstrom et al., 1968); they affect the cardiovascular system, acting as pressor agents under some circumstances and as depressor agents under others

(Carlson, 1967). Prostaglandins are associated with the nervous system and apparently are released from nerve endings during stimulation (Horton and Main, 1966; Coceani et al. 1967). They also have important relationships in lipid and carbohydrate metabolism (Bergstrom, 1967). In addition, it has been suggested that prostaglandins may serve as general modifiers of adenyl cyclase activity in a number of tissues (Bergstrom, 1967).

Prostaglandins are distributed throughout the body. In the reproductive tract, they have been identified in the ovary (Wilks et al., 1972), uterus (Harrison et al., 1972; Poyser, 1972; Wilson et al., 1972), decidual tissue (Karim and Devlin, 1967), menstrual fluid, placenta (Pickles, 1967) and ammiotic fluid (Karim and Devlin, 1967). Human semen is the richest natural source of prostaglandins (von Euler, 1967). Another characteristic of prostaglandins is that they are not stored to any extent in the tissues (Ramwell and Shaw, 1971), but many stimuli, including simple handling, cause their prompt release (Piper and Vane, 1971). Prostaglandins have a relatively short half-life in the circulation, usually believed to be only a few minutes (Raz, 1972). One reason for this short life is rapid metabolism in the lungs, liver and other tissues (Piper and Vane, 1971).

As previously stated one of the most notable affects of prostaglandins (in this case $PGF_{2\alpha}$) in the field of

reproduction is the ability to cause a decrease in progesterone secretion from an ovary containing a corpus luteum i.e., a luteolytic effect. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), a primary prostaglandin with two double bonds (5-6 and 13-14) and three hydroxyl groups (9, 11 and 15), was first demonstrated to have a luteolytic effect by Pharris and Wyngarden (1969) and by Blatchley and Donovan (1969). Pharris and Wyngarden (1969) reported that the intrauterine infusion of $PGF_{2\alpha}$ into pseudopregnant rats for 2 days resulted in a sharp decrease in plasma progesterone while Blatchley and Donovan (1969) observed that $PGF_{2\alpha}$ injections caused morphological degeneration of the corpora lutea of hysterectomized guinea pigs. Futher work demonstrated this action of $PGF_{2\alpha}$ in rabbits (Duncan and Pharris, 1970), hamsters (Labhsetwar, 1971) and mice (Labhsetwar, 1972).

The most convincing evidence for the luteolytic effect of $PGF_{2\alpha}$ in farm animals was obtained in sheep having ovarian autografts in the neck. (Chamley et al., 1972; Goding et al., 1972). Infusion of $PGF_{2\alpha}$ into the ovarian artery resulted in a prompt decline in the progesterone output and eventual degeneration of corpora lutea.

In cattle the injection of 5 mg of $PGF_{2\alpha}$ into the uterus of cows for 2 days beginning on day 4 of the cycle, or a single subcutaneous injection of 30 mg, induced luteal regression and premature estrus (Lauderdale, 1972; Rowson et al., 1972). When $PGF_{2\alpha}$ was administered before day 5,

the treatment proved less effective. Recently, Lauderdale et al. (1974) utilized a total of 208 cows located in four different states to investigate the effect of $PGF_{2\alpha}$ on fertility. The day of the estrous cycle was unknown for most of the cattle used in the study, therefore the injection of $PGF_{2\alpha}$ was based on palpation of the ovaries for the presence of corpora lutea. Estrus was induced in 64% (155 of 239) of the cattle receiving $PGF_{2\alpha}$. Fertility was similar to controls (53%) when cattle were inseminated at the synchronized estrus following $PGF_{2\alpha}$ treatment (52%) and when the females were inseminated at predefined intervals (72 and 90 hr.) following injection of the compound (55%). In a similar study, Welch et al. (1975) infused 1 or 2 mg of $PGF_{2\alpha}$ into the uterus of 67 lactating beef cows during the luteal phase of the cycle and concluded that the drug was effective in synchronizing estrus without adversely affecting conception.

The effect of $PGF_{2\alpha}$ on luteal function in gilts has been studied by Hallford et al., (1975). Gilts were injected four times intramuscularly at 12-hr. intervals starting on day 4 or 12 of the estrous cycle for a total of 80 mg of $PGF_{2\alpha}$. When treatment was initiated on day 12, gilts had shorter estrous cycles than controls and plasma progesterone was reduced. Neither estrous cycle length nor progesterone concentration was altered when $PGF_{2\alpha}$ was administered on day 4.

The effect of $PGF_{2\alpha}$ on the corpus luteum of mares was first demonstrated by Douglas and Ginther (1972) who found that as little as 1.25 mg of $PGF_{2\alpha}$ (approximately 6 ug/kg of body weight) injected subcutaneously on day 6 of the cycle, induced premature estrus in pony mares. The mean length of diestrus was shorter for the 12 $PGF_{2\alpha}$ treated mares than for the three control females. All of the treated mares returned to estrus 3 or 4 days following $PGF_{2\alpha}$ treatment and ovulated.

A similar luteolytic effect was demonstrated in the mare by Noden et al. (1974) and by Douglas and Ginther (1975a,b) following the administration of $PGF_{2\alpha}$-tham salt (1.34 mg $PGF_{2\alpha}$ - tham salt is equivalent to 1.00 mg $PGF_{2\alpha}$ free acid). The former workers infused $PGF_{2\alpha}$ - tham salt into the uterus (IU) or injected it subcutaneously (SC) in six mares 7 to 9 days following ovulation and observed that blood progesterone fell from a mean pretreatment level of 13.6 ng/ml to .9 ng/ml within 48 hr posttreatment (Noden et al., 1974). Estrus began 2.2 days after $PGF_{2\alpha}$ treatment and ovulation occurred at day 5.8 of heat. Noden et al. (1974) observed that the estrus after $PGF_{2\alpha}$ treatment persisted longer than heat in control cycles (7.5 vs. 5.2 days). However this longer duration of estrus in mares following $PGF_{2\alpha}$ treatment has not been reported by other workers. No differences in luteolysis, estrus or ovulation were observed between the two routes of administration (IU or SC).

Douglas and Ginther (1975a) administered $PGF_{2\alpha}$ - tham salt (.25 or 1.25 mg) via three different routes (intramuscular, intrauterine, intraluteal) to 27 pony mares on day 7 postovulation and observed a significant decrease in plasma progesterone concentration by 24 hr. following treatment with the compound. Results indicated that local administration (intrauterine or intraluteal) did not improve the luteolytic efficacy of $PGF_{2\alpha}$ over systemic administration (intramuscular). The interval from treatment to estrus was 5.9 days for mares given .25 mg, 3.9 days for those given 1.25 mg of $PGF_{2\alpha}$ and 13.3 days for controls. Also the interval from treatment to ovulation and the interovulatory interval was significantly shortened in mares given 1.25 mg $PGF_{2\alpha}$ but not in mares given .25 mg of the compound. In a related study, Douglas and Ginther (1975b) observed that the interval from treatment to ovulation and the interovulatory interval tended to decrease as the dose of $PGF_{2\alpha}$ increased. Both estrus and ovulation appeared to be synchronized when mares were given $PGF_{2\alpha}$ on day 7, 10 or 13 postovulation, but not in mares given the compound on days 1 or 4 after ovulation or on day 2 of estrus. In addition the interovulatory interval was shortened only when $PGF_{2\alpha}$ was given on day 4 or day 7 following ovulation.

Although the foregoing studies demonstrate that $PGF_{2\alpha}$ - tham salt causes luteolysis and could be used to control the estrous cycle of the mare, Lauderdale et al. (1975a)

observed that the commercial form of $PGF_{2\alpha}$ - tham salt, Prostin $F_{2\alpha}$alpha® caused side effects in 54 mares as manifested by a sweating response and an associated reduction in rectal temperature when administered at the dose rate of 1 to 10 milligrams. A general positive relationship existed between degree of sweating and $PGF_{2\alpha}$ dose. Sweating started about 15 min. after $PGF_{2\alpha}$ injection and ceased approximately 2 hr. following injection. In a subsequent study Lauderdale et al. (1975b) injected six mares with either 10 mg $PGF2_{\alpha}$ (Prostin F_2 alpha®) or 10 mg epinephrine and observed that females treated with $PGF_{2\alpha}$ sweated but did not shiver and those treated with epinephrine sweated but did shiver. Plasma epinephrine and nonepinephrine levels were elevated 15 min. following $PGF_{2\alpha}$ injection. The authors suggested that $PGF_{2\alpha}$ related sweating was associated with release of epinephrine from the adrenal medulla and the decrease in rectal temperature in the $PGF_{2\alpha}$ treated mares was caused by sweating in the absence of shivering.

Since the discovery of the luteolytic effect of $PGF_{2\alpha}$ several prostaglandin analogues have been synthesized. Three of these analogues, ICI 79939, ICI 81008 and RS 9390 have been tested in mares (Allen and Rowson, 1973; Allen and Rossdale, 1973; Allen et al., 1974; Berwyn-Jones and Irvine, 1974; Thompson and Witherspoon, 1974; Lamond et al., 1975; Tolksdorff, 1975; Witherspoon et al., 1975). Allen and Rowson (1973) using 14 pony mares demonstrated the high luteolytic potency of the $PGF_{2\alpha}$ analogue ICI-79939.

A high degree of lutolytic activity was observed when 100 to 600 ug of the compound was administered between the fourth and thirteenth day of diestrus. Estrus occurred 3 days from the start of treatment and all mares ovulated normally. Ovulation occurred on the average 10 days from the first dose of the analogue. A fall in the level of progesterone was observed before the return of estrus. Mares treated on day 2 and day 3 of diestrus did not respond to prostaglandin treatment indicating that the corpus luteum of the mare is not susceptible to luteolytic attack until at least 3 days postovulation. At the 600 ug dose level the compound caused sweating in the ventral regions of the neck, chest and abdomen, hypermotility of the gastro-intestinal tract leading to watery diarrhea, increased rates of pulse and respiration and mild colic. These symptoms occurred most strongly 18 to 22 min. after injection and persisted for 2 to 4 hours. Similar side effects were observed by Allen and Rossdale (1973) who demonstrated the clinical value of ICI-79939 for inducing luteolysis in thoroughbred mares in which persistent luteal function prevented the onset of estrus. Thirty-four of 38 nonpregnant, non-cycling mares came into heat within 3 days of treatment with the $PGF_{2\alpha}$ analogue and subsequently ovulated.

Another synthetic analogue of $PGF_{2\alpha}$ that has been studied in the mare is ICI-81008. In laboratory species this compound is less potent as a luteolytic agent than

ICI-79939 but is considerably less toxic (Allen et al., 1974). No toxic effects were observed in 25 Welsh pony mares injected intramuscularly with 80 to 250 ug of the $PGF_{2\alpha}$ analogue, but all of the females (28) given 750 to 4,000 ug of the drug developed mild sweating and one mare (4,000 ug dose) developed diarrhea and mild colic (Allen et al., 1974). The researchers emphasized that the 750 ug dose was six times the miminal amount needed (125 ug) to induce luteolysis in the pony mares. All of the mares (19) given the drug between day 4 and day 11 of diestrus returned to estrus by the fourth day after treatment and all but two of these females ovulated during the induced estrus. Progestagen levels in the mares dropped rapidly within 48 hr. of treatment with the compound. Allen et al., (1974) also tested the therapeutic use of ICI-81008 using thoroughbred mares that were in prolonged diestrus and observed that in 63 treated mares, 55 came into estrus within 4 days of treatment with the analogue and subsequently ovulated. They also noted that 40% of the mares mated conceived during the induced estrus. In a similar study, Berwyn-Jones and Irvine (1974) injected 99 mares which had not shown estrus for 5 weeks to 8 years with the compound and found that estrus was induced within 5 days in 74% of the the females. The conception rate in 59 mares mated at the induced estrus was 64%. Elevated blood progesterone levels before treatment indicated a functional corpus luteum as the cause of suspension of cycling in the majority of mares (Berwyn-

Jones and Irvine, 1974). Progesterone concentrations of these mares fell to basal levels 4 days after injection with the $PGF_{2\alpha}$ analogue. These studies indicate that ICI-81008 causes luteolysis in mares without significant clinical side effects. Also, because conception rate at the induced estrus was not impaired, it appears that the treatment has no adverse effects on fertility.

The luteolytic effect of the prostaglandin $F_{2\alpha}$ analogue RS 9390 has also been tested in mares. This analogue causes luteolysis, as determined by its ability to reduce peripheral plasma progesterone levels, in cycling non-lactating mares (Thompson and Witherspoon, 1974; Witherspoon et al., 1975) anestrous mares (Lamond et al., 1975) and lactating postpartum mares (Tolksdorff, 1975; Witherspoon et al., 1975).

For cycling non-lactating mares (Thompson and Witherspoon, 1974; Witherspoon et al., 1975) the effective RS 9390 dose ranged between 1.0 and 4.0 mg and was given to 25 females 8 to 10 days after ovulation. The mares usually returned to estrus 1.5 to 5 days and ovulated about 7 days following treatment. Eight of nine cycling non-lactating mares bred at the induced estrus were fertile (Witherspoon et al., 1975).

A dose of 2.0 mg of RS 9390 given to anestrous mares (Lamond et al., 1975) with initial plasma progesterone concentrations greater than 1.0 ng/ml caused luteal regression.

In most cases the mares were observed in estrus 2 to 4 days after treatment and ovulated between 4 and 8 days following treatment. Lamond et al., (1975) stated that fertility at the induced estrus was "satisfactory".

The injection of lactating postpartum mares with RS 9390 8 to 10 days after ovulation resulted in a rapid fall in progesterone levels during the first 48 hr. post-treatment (Tolksdorff, 1975; Witherspoon et al., 1975). Most lactating postpartum mares came into estrus 5 days after injection of the analogue and subsequently ovulated. Conception rates during the RS 9390 induced estrus were 81 and 77% for the Tolksdorff (1975) and Witherspoon et al., (1975) studies, respectively.

The foregoing studies demonstrate that $PGF_{2\alpha}$ is luteolytic in the cow, ewe, sow and mare and suggest that it could be used to synchronize the estrous cycle of these species. The synchonization of estrus means that the estrous cycle is altered so that the estrus period of many females is caused to occur on the same day or within a period of 2 or 3 days (Lasley, 1968). This has several practical advantages for the cattle, sheep and swine producer. The concentration of the breeding period within 2 or 3 days would save time and labor, and would make it possible to breed more females to a superior progeny-tested sire. The offspring would not have to be segregated into age groups during the growing and fattening period since they would

be about the same age and time of parturition and marketing would be more concentrated (Hafez, 1968). Estrus synchronization, according to the previously stated defination, would not be practical or advantageous for the horse producer. Since the insemination of mares with stored semen has not been perfected and is not allowed by the major breed associations it would be impractical to breed a large number of females within a period of 2 or 3 days using natural mating. However, the control of estrus and ovulation would be helpful to the horse producer by reducing some of the variation in the reproductive patterns of the mare and allow breeding at a time when there is the highest likelihood of fertility. The estrous contol compound $PGF_{2\alpha}$ would be helpful in preventing the difficult situation which often occurs on large breeding farms when many mares booked to be covered by a single stallion, come into heat at the same time. The compound could also be used to reduce the valuable time which is lost by broodmares as they pass through diestrus.

One of the most logical uses of $PGF_{2\alpha}$ would be to induce estrus in mares shortly after foal estrus and thus shorten the postpartum interval while avoiding the practice of breeding on foal heat. Mares are usually bred on foal heat in order to get foals as early in the year as possible and to avoid the problem of lactational diestrus. However a review of the literature reveals that breeding mares on foal estrus is detrimental to fertility.

Foal Estrus. Among the domesticated animals early postpartum estrus is peculiar to equidae, swine and the bactrian camel. The later is generally in heat the day after calving and ovulates 3 to 5 days before the end of estrus (Asdell, 1964). The sow exhibits a heat period shortly after parturition (3 to 5 days), but she is infertile at this estrus because ovulation does not occur. However fertile heat generally follows a week after the pigs are weaned (Lasley, 1968). The interval from parturition to first estrus in the bovine averages between 50 and 60 days with some cows showing a much longer interval (Lasley, 1968). In ewes heat does not ordinarily occur during lactation (Lasley, 1968). Early postpartum heat is a feature of the sexual cycle of certain rodents, marsupials and seals (Asdell, 1964). In the guinea pig estrus occurs within 2 hr. of the end of parturition (Asdell, 1964). The factors which determine whether a species exhibits the phenomenon or not are unknown, and even within a genus some members experience it while others do not (Asdell, 1964).

In the mare foal estrus is complete, that is, it is accompanied by ovulation. It has been erroneously accepted by many horse breeders that: foal heat is the most opportune time to get a mare in foal; foal heat occurs persistently on the ninth day after foaling; and, even if a mare is not in heat on day 9, she should be force bred and would conceive anyway (Berliner, 1959).

Several researchers have reported that although foal heat is a regular occurrence in practically all foaling mares, it is subject to the typical variability with respect to both the time of onset and to duration as any other reproductive phenomenon of the mare (Constantinescu and Mauch, 1938; Cummings, 1942; Jennings, 1950; Mahaffey, 1950; Trum, 1950; Arora and Luktuke, 1972). In fact, Cummings (1942) observed more variation in all phases of foal estrus than in subsequent estrus periods.

Typical of this variability is the interval from foaling to the onset of foal estrus. Constantinescu and Mauch (1938) studied, 1,366 foalings and observed that heat occurred between the fourth and seventeenth day after parturition with a mean of nine. In 90% of the cases, foal heat occurred between the seventh and eleventh day postpartum. The authors stated that estrus periods starting later than 20 to 40 days after foaling should be considered regular cyclic estrus periods, and that the longer intervals are caused by skipped or unnoticed foal heats. Trum (1950) studied the reproductive activity of mares maintained at an army remount depot and observed that 93% of the mares showed estrus 5 to 18 days after foaling, with 77% showing between the seventh and tenth day postpartum. Seventy percent of the mares, including those that had exhibited estrus earlier, were in heat on the ninth day following foaling. The authors emphasized that it was impossible to find so many mares willing to accept the

stallion on any other specific day during the estrous cycle. Although these findings would seem to speak strongly in favor of breeding on foal heat and lend support to the practice of breeding on day 9, actual breeding results do not bear this out. Caslick (1937) reported that of 301 mares mated on day 9 postpartum, 37% conceived at this breeding. In a later study, Trum (1950) mated 56 healthy mares during foal estrus and only 43% conceived. The conception rate in mares which did not conceive and were rebred at the next estrus was 75%. Similar findings utilizing the records of 181 mares have been reported by Jennings (1950) who noted that breeding on foal heat resulted in a four fold increase in abortions, 15% cases of dystocia and six times as many dead-born and nonviable foals. Despite these detrimental effects the practice of breeding on foal estrus persists because most breeders are intent on having foals born as close as possible to the universal birthdate of January 1.

Contributory information as to why conception rate is low when mares are bred on foal estrus was provided by Andrews and McKenzie (1941) who observed that the uterine epithelium after foaling had rarely returned to normal within 10 days, but that complete restoration usually had occurred from 13 to 25 days postpartum. Because foal heat occurs most frequently between the seventh and eleventh day postpartum (Constantinescu and Mauch, 1938; Trum, 1950), the uterus has had insufficient time for complete involution.

Since minimum time loss between foaling and conception is necessary in efficient horse production, passing foal heat and administering synthetic or natural $PGF_{2\alpha}$ during the subsequent luteal phase to induce estrus may permit more complete involution of the uterus and a greater chance of conception and normal pregnancy than that which exists at the first postpartum estrus. The induction of estrus with $PGF_{2\alpha}$ after foal heat would also be helpful in preventing the long periods of diestrum which sometimes follow unsuccessful foal estrus breedings. Day (1939) stated that prolonged diestrus was one of the greatest irregularities in foaling mares and was most common in mares in poor flesh and heavy milkers. Britton and Howell (1945) studied the breeding history of 36 broodmares from 1927 to 1943 and found that failure to show estrus after unsuccessful foal heat breedings was manifested a total of 23 times by 15 mares. The average duration of diestrus was 5.1 months with the 13 heavy milkers showing a longer diestrum (6.5 months) than the two poor milkers (2.5 months). Four of the 15 mares repeated the irregularity twice and two repeated it three times.

A review of the literature revealed little information on the causes of equine abortion but did show that breeding mares on foal heat is detrimental to fertility and demonstrated that $PGF_{2\alpha}$ is a powerful luteolysin when administered during the luteal phase of the cycle. This review served

as a basis for the present two experiments which were designed to determine the endocrine status of the peri-parturient mare (Experiment I) and to assess the possibility of using $PGF_{2\alpha}$ to control estrus in the foaling mare (Experiment II).

CHAPTER III

EXPERIMENTAL PROCEDURE

Two experiments consisting of two trials each were conducted during the breeding seasons of 1974 and 1975 at the Louisiana State University Horse Unit located at Baton Rouge, Louisiana. The experiments were conducted to monitor the endocrine status of the periparturient mare and to determine if prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) could be used to induce estrus in mares shortly after foal heat.

Experiment I. Plasma Progestin, Estrogen and Corticoid Levels in the Mare and Newborn Foal.

Experiment I was designed to determine the peripheral progestin, estrogen and corticoid levels in the mare at parturition and in the newborn foal. In trial 1, nine Quarter Horse mares ranging in age from 5 to 18 years which were bred to one of two Quarter Horse stallions were used as experimental animals. During gestation the mares were grazed on a bahia and coastal bermudagrass pasture overseeded with ryegrass. When needed, additional forage was supplied in the form of high quality bermudagrass hay. In order to facilitate blood sample collections, mares were kept in a 6 ha paddock during the final 14 days prior to their expected foaling date. During this time of confinement prepartum mares were maintained on Coastal bermudagrass hay and alfalfa hay supplemented with approximately 2 kg of grain (12% crude protein) per head

per day. Blood samples (20 ml each) for hormone determinations were collected by jugular puncture four times daily at 0600, 1200, 1800 and 2400 hr. from 7 days prior to parturition through 2 days postpartum. The mares were restrained with a rope halter and if necessary were placed in palpation stocks during blood collection. Mares were allowed to foal in the paddock. A 10 ml blood sample was also collected by jugular puncture from each of nine foals (five colts and four fillies) within 3 hr. of birth and on six foals (three colts and three fillies) at 24 hr. postpartum. Blood samples were collected into 10 ml vacuum tubes[1] containing sodium heparin as the anticoagulant. Samples were centrifuged and plasma stored in glass screw-cap vials at -20C until assayed.

Plasma progestin and corticoid levels were determined on blood samples using the competitive protein binding assay of Murphy (1967) and Neill et al. (1967) with minor modifications as described by Goodeaux (1975). Individual sample recoveries were obtained on 20% of the assay samples selected at random by adding approximately 2000 cpm of 1, 2, 6, 7 -^{3}H progesterone and 1, 2, 6, 7 -^{3}H corticosterone[2] to extraction tubes before addition of the plasma. Mean progesterone and

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[1] Vacutainer Brand, Becton-Dickinson, Rutherford, N.J.

[2] New England Nuclear, Boston, Mass.

corticoid recovery rates were 101 $\pm$ 1.7 % and 89 $\pm$ 0.4%, respectively. Non-hemolyzed, male dog plasma was the source of corticoid binding globulin (CBG). The CBG was diluted to a 3% stock solution with sodium phosphate buffer (pH 7.35, .04M). Approximately 40 nCi of 1, 2, 6, 7 - ^{3}H corticosterone was added to each assay tube in 1.0 ml of CBG solution for both progestin and corticoid determinations. A plasma volume of .65 ml was first extracted with 6.0 ml of nanograde petroleum ether for progestins. Subsequently corticoids were extracted with 6.0 ml of nanograde dichloromethane. Sample residues were reconstituted with absolute ethanol and assayed in duplicate. Fuller's earth[3] was used to separate the bound from the free hormone fractions. The earthen material in twice deionized water and chilled to 4C was constantly stirred with a magnetic bar and added to the assay tubes as a suspension. A hand pipet[4] was used to add the suspension (40 mg/ml, .5 ml/tube) and the Fuller's earth was precipitated by centrifugation. A 10 ml volume of scintillation fluid[5] was added and vials were stored in a dark room for at least 8 hr. prior to

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[3]Fuller's Earth, F-200 Mesh, Sigma Chemical Co., St. Louis, Mo.

[4]Micro/pettor 10556, Scientific Manufacturing Industries, Emeryville, Calif.

[5]Ready-Solv Solution VI. Beckman Instruments, Inc., Fullerton, Calif.

counting. All assayed unknowns were counted on a Beckman LS-233 liquid scintillation counter for 2 min/each. Pooled mare plasma was analyzed with the assay.

Total plasma estrogen levels were determined by radioimmunoassay (RIA). Radioimmunoassays take advantage of antibody-antigen reactions, where the antigenic ligand is bound to gamma globulin proteins. Very high sensitivity is possible providing a high affinity antibody can be formed against a highly purified ligand substance. Radiolabelled antigen-antibody bound or free fractions can be used for quantitation of natural antigens by comparison with corresponding fractions in standard tubes containing known amounts of unlabelled antigen (Skelley et al., 1973).

The antibody used for determination of total estrogens in the present system was formed in rabbits against estradiol-17β conjugated at the number 17 carbon to bovine serum albumin (E-17 antibody, generously supplied by Dr. Norman R. Mason, Lilly Research Laboratories, Indianapolis, Indiana 46206). Cross reactions of the antibody with various steroids were determined for two different levels of added steroid, 100 and 1000 pg and the results are summarized in table 1. Percent cross reaction is here defined as:

$$\frac{\text{pg detected as "total estrogen"}}{\text{pg added steroid}}.$$

The antibody used in the present experiment detects primarily estrone and estradiol.

TABLE 1. CROSS-REACTIONS OF E-17 ANTIBODY FOR TOTAL ESTROGENS

Steroid	Amount added steroid (Cross-reaction, %)	
	100 pg	1000 pg
Estrone	100	100
Estradiol	75	75
Estriol	10	4
Equilin	13	7
Equilenin	16	11
Corticosterone	0	1
Progesterone	0	1
Testosterone	0	1

Total plasma estrogens were separated from other hormones and proteinaceous substances found in equine plasma by a modification of the solvent partition extraction procedure described by Goodeaux (1975). All extractation and assay glassware was soaked in a soap solution[6], well rinsed in tap water and distilled deionized water and oven dried before use. Two 1.5 ml aliquots of plasma from each sample were delivered into two 16 x 25 mm disposable, screw cap culture tubes using an adjustable microliter pipette[7]. A .1 M sodium phosphate buffer[8] (pH 7.2) was used to rinse the instrument between pipetting each plasma sample. The estrogen fraction of the sample was extracted by adding 12 ml of anesthesia grade diethyl ether[9] to the plasma and duplicate. The samples were then mixed and centrifuged according to the procedure of Goodeaux (1975). The solvent phase of each tube was separated from

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[6] 1 % solution of 7 X concentrate, Limbro Chemical Co., New Haven, Conn.

[7] Pipetman adjustable microliter pipette (adjustable from 200 to 1000 ul), Rainin Instrument Co., Brighton, Mass.

[8] $Na_2HPO_4 \cdot 7H2O$, Fisher Scientific Co., Fair Lawn, N.J.; $NaH_2PO_4 \cdot H_2O$, J. T. Baker Chemical Co., Phillipsburg, N.J.

[9] Diethyl ether, ether for anesthesia, Mallinckrodt, Inc., St. Louis, Mo.

the aqueous plasma phase after snap freezing the plasma layer at -40°C in an isoproyl alcohol and dry ice bath. The supernatant containing the estrogen fraction was decanted into two 16 X 100 mm tubes and evaporated to dryness in a 40 C water bath with a gentle stream of filtered room air. Absolute ethanol[10] (1.0 ml) was added to the dried solvent fraction in order to resuspend the estrogen extract. After thorough mixing, a .75 ml aliquot was taken (Pipetman pipette[7]) from each sample and its duplicate and placed separately into two 10 x 75 mm culture tubes, covered with parafilm and stored at -15C inside a plastic bag until assayed.

The buffer used in the total estrogen RIA was .1 M sodium phosphate[8] (pH 7.2) with .1% bovine γ- globulins[11] added. This buffer was used to dilute antibody and labelled estrogen and to suspend charcoal.

Unknowns were compared to standards of estrone[12] in absolute ethanol[10]. Standard amounts used were 0, 10, 20, 35, 50, 75, 100, 200, 350, 500, 750 and 1000 pg estrone in .1 ml ethanol, prepared from dilutions from a stock of 1 ug/ml. Tubes (10 x 75 mm) were prepared for addition of

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[10] Ethanol-Reagent Grade, U. S. Industrial Chemicals Co., New York, N.Y.

[11] Cohn Fraction II, Sigma Chemical Co., St. Louis, Mo.

[12] Sigma Chemical Co., St. Louis, Mo.

standards by evaporation of an amount of the extraction solvent equal to that used for preparation of the volume of sample to be assayed, to correct for any solvent blank values. Standards were then pipetted[13] into the tubes and treated as the samples through the remainder of the assay.

On the day preceding the assay the ethanol fraction was removed from the plastic bag and air dried in a 40 C water bath. After thorough drying, a .5 ml aliquot of E-17 antibody (diluted 1: 20,000) was added to each culture tube. The samples were then mixed on a vortex mixer and incubated for 15 minutes in a 40 C water bath, remixed and placed in a refrigerator (4C) for 12 to 18 hours. Following incubation ^{3}H-Estradiol[14] was added to each assay tube (25 nCi, or 140 pg/tube in .2 ml buffer), mixed and incubated for 2.5 to 3.5 hr. in a refrigerator (4C).

Dextran-coated charcoal (1.25 mg charcoal[15] + 1.25 mg Dextran T-70[16] per tube in .3 ml) was the absorbent used to separate the unbound hormone fraction. It was mixed with a magnetic stirrer in an ice water bath for a minimum of 30 minutes before use. During the assay the

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[13]Micro/pettor 1075-E, Scientific Manufacturing Industries, Emeryville, Calif.

[14]Estradiol-17B-6, 7-^{3}H(N), 47.9 Ci/m mol, New England Nuclear, Boston, Mass.

[15]Activated Charcoal (Neutralized), Sigma Chemical Co., St. Louis, Mo.

[16]Dextram T 70, Pharmacia Fine Chemicals, Uppsola, Sweden.

charcoal was maintained on ice and constantly stirred with a magnetic stirrer. Each rack of 60 to 65 tubes was chilled in an ice bath 10 to 20 minutes prior to and during addition (Pipetman pipette[7]) of dextran-coated charcoal suspension to each assay tube. Tubes were mixed thoroughly and the charcoal allowed to settle for a total reaction time of 15 minutes while maintained in an ice bath. The charcoal was separated by centrifugation (3,000 rpm) at 4C for 12 minutes.

A dilutor[17] was used to aspirate .75 ml of sample which was then mixed with 7.5 ml of scintillation fluid[5] in low potassium glass scintillation vials (22 mm cap). Vials were wiped clean with 50% isopropyl alcohol and stored in the dark for approximately 8 hr. prior to counting to avoid photoluminescence in the scintillation fluid. Samples were counted a maximum of 5 minutes each on a Beckman LS-233 liquid scintillation counter using a wide tritium window at 1.5% preset error.

Extraction efficiency was monitored in approximately 8% of the samples. Recoveries were done by adding approximately 1200 cpm of ^{3}H-estradiol to 16 x 125 mm extraction tubes before plasma addition and extracted as usual.

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17 Repipet Dilutor, Labindustries, Berkeley, Calif.

Recovery samples were carried through all solvent and glassware steps and an aliquot of the final ethanol fraction dried in a scintillation vial before addition of scintillation fluid and counting.

Standard curves were constructed by calculating a simple regression between the natural log of the standard concentration and counts (cpm) antibody-bound. A Monroe 1775 Calculator[18] was programmed with slope and intercept values and total estrogen levels in pg/ml plasma were computed from counts (cpm) bound, figuring in appropriate corrections for dilution and recovery loss.

In trial 2 the experimental animals consisted of nine Quarter Horse mares varying in age from 3 to 12 years and bred to a Quarter Horse stallion. Data in trial 2 were collected the same as for trial 1 with the following modifications. Mares in trial 2 were grazed exclusively on a permanent grass pasture until December when they were rotated every 12 hr. between a permanent and a ryegrass pasture. In order to minimize disturbance of the experimental animals, the mares in trial 2 were allowed to remain on pasture throughout the gestation period except for a brief time during blood sample collections when they were

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[18] Monroe Model 1775 Calculator, Monroe, The Calculator Company, Orange, N. J.

placed in a stall and restrained with a rope halter. Blood samples (20 ml each) were collected twice daily at 0800 and 2000 hr. from 7 days prepartum to 2 days postpartum. Mares were allowed to foal in the pasture. A 10 ml blood sample was obtained from each of nine foals (four colts, five fillies) within 6 hr. of birth and at 24 and 48 hr. postpartum.

Circulating progestin and corticoid levels in trial 2 were determined using the same competitive protein binding assay described for trial 1 with slight modifications. Mean progesterone and corticoid recovery rates for trial 2 were 67% and 100%, respectively. The CBG used in the second trial was diluted to a 4.5% stock solution with sodium phosphate buffer and corticoids were extracted with 6.0 ml of nanograde diethyl either. The solvent phase containing extracted progestins or corticoids was separated from the aqueous plasma phase by snap freezing the plasma layer at -40C in an isopropyl alcohol and dry ice bath. An adjustable microliter pipette[7] was used to add Fuller's earth to the assay tubes. Labelled antigen used was 1, 2 - ^{3}H - corticosterone (100 nCi/tube). Pooled cow plasma was analyzed with the assay. Estrogen levels in trial 2 were determined using the same RIA procedure described for trial 1.

Least squares analysis of variance (Harvey, 1960) was applied to the data to determine the effect of mare, time of blood collection, day and time by day interaction on

progestin, estrogen and corticoid levels. Linear contrasts among the day means were included to further define the trend of hormone levels before, during and after parturition. Least squares analysis of variance was also used to test for differences in foal plasma hormone levels.

Experiment II. Induction of Estrus in Mares after Foal Heat with Prostaglandin $F_{2\alpha}$.

Since several workers have reported detrimental effects of breeding mares on foal heat, two trials were designed to assess the possibility of inducing estrus with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) shortly after foal estrus, thereby reducing the interval from foaling to rebreeding.

In the spring of 1974 (trial 1) a total of 14 Quarter Horse mares ranging in age from 5 to 13 yr. were assigned to the study. The mares were grazed on a permanent pasture consisting of clover, bahia, dallas and coastal bermudagrass. Following parturition, mares were checked daily for foal estrus using a combination of pasture, corral and bar teasing. The pasture method was used in order to simulate "natural" conditions and consisted of riding an experienced stallion among a band of mares and permitting the stud to tease the females at will. In the second procedure a teaser stallion was placed in a corral, with the mares in a surrounding paddock. The third method entailed leading each mare to a barrier (bar) between the mare and

stallion and allowing the stallion to tease. Whenever a stallion became lethargic he was replaced. Estrus was based on the following criteria: tail raising, squatting, urinating and eversion of the vulvar labia (winking). Mares were rectally palpated daily during foal estrus to detect ovulation. On day 6 and 7 after foal estrus, five mares were given 15 mg subcutaneous (SC) injections of $PGF_{2\alpha}$ - tham salt[19] and four mares were injected with 10 mg (SC) injections of $PGF_{2\alpha}$ free acid[20] (1.34 mg of $PGF_{2\alpha}$ - tham salt is equivalent to 1.00 mg of $PGF_{2\alpha}$ free acid). Control mares were injected with an equal volume of sterile saline. Blood samples (10 ml) for progestin determination were collected by jugular puncture 15 min. prior to and following each $PGF_{2\alpha}$ injection and each day thereafter until detection of estrus. The samples were collected into evacuated glass tubes containing sodium heparin as the anticogulant and the plasma stored at -20C in glass screw cap vials until assayed. Progestin concentrations for the $PGF_{2\alpha}$ treated mares were determined using the competitive protein binding assay described for trial 1 of the first experiment.

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[19] $PGF_{2\alpha}$ - tham salt, The Upjohn Company, Kalamazoo, Mich.

[20] $PGF_{2\alpha}$ - free acid, G. D. Searle and Company, Chicago, Ill.

Mares were observed for side effects after each $PGF_{2\alpha}$ treatment and were heat checked employing the methods previously described at least once a day following injections of $PGF_{2\alpha}$ or sterile saline. Those detected in heat were rectally palpated daily to determine time of ovulation. All mares in trial 1 were handmated to a Quarter Horse stallion (LSU #10).

A total of 16 Quarter Horse mares ranging in age from 3 to 30 yr. were used in trial 2 to determine the effect of Prostin $F_{2\alpha}$® [21] on the estrous cycle of the postpartum lactating equine female. Following parturition the mares were checked daily for foal estrus as described for trial 1 and palpated daily during foal heat to detect ovulation. Six and 7 days following the end of foal estrus, nine mares were injected subcutaneously (SC) with 15 mg of Prostin $F_{2\alpha}$® and the seven control mares were given an equal volume (3 ml) of sterile saline. Blood samples for progestin determination were obtained by jugular puncture 15 min prior to and following each Prostin $F_{2\alpha}$® or saline injection and each day thereafter until detection of estrus. Subsequent procedures followed in the storage of blood samples, determination of progestins, and detection of

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[21] Prostin F_2 alpha® (dinoprost tromethamine), The Upjohn Company, Kalamazoo, Mich.

estrus and ovulation were the same as those described for trial 1. Eight treated and five control mares were hand-mated to the stallion LSU #20 while one treated and two control females were mated to LSU #10. Mares in both trials were rectally palpated 60 days following the last breeding to confirm pregnancy.

Statistical analyses of data were performed using least squares procedures as outlined by Harvey (1960).

CHAPTER IV

RESULTS AND DISCUSSION

Two experiments consisting of two trials each were conducted to determine the endocrine status of the peri-parturient mare and newborn foal (Experiment I) and to assess the possibility of using prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) to control the estrous cycle of the postpartum mare (Experiment II). The results of each study will be presented separately and a general discussion will follow in which the results will be brought to bear upon the problem of poor reproductive efficiency in mares.

Experiment I. Plasma Progestin, Estrogen and Corticoid Levels in the Mare and Newborn Foal.

Although the endocrine status of the mare during gestation has been studied to some extent, to our knowledge no systematic work has been done to characterize the blood profile of progestins, estrogens and corticoids at the time of parturition. A comparison of these hormone levels in "normal" foaling mares with those that habitually abort may lead to a greater understanding of the causes of equine abortion.

Trial 1. In the initial trial, blood samples for hormone determination were collected from nine mares four times daily at 0600, 1200, 1800 and 2400 hr. from 7 days

prepartum through day 2 postpartum. Least squares analysis of variance revealed a difference ($P < .01$) in progestin levels among days and mares. The mean progestin concentrations in blood of prepartum mares remained relatively stable (between 10 and 13 ng/ml) from day 7 through day 3 prepartum (table 2). Linear contrasts among the day means revealed a decline ($P < .01$) in progestin concentrations from 13.4 $\pm$ .6 ng/ml on day 3 prepartum to 3.2 $\pm$ .5 ng/ml on the day of parturition (figure 1). A drop ($P < .01$) in progestins also occurred from day 1 prepartum (9.7 $\pm$ .5 ng/ml) to the day of foaling. Levels among mares varied ($P < .01$) from a mean of 7.1 $\pm$ 1.4 ng/ml to a mean of 12.9 $\pm$ .5 ng/ml (table 3). The trend in progestin levels in this trial is similar to that reported by Smith (1974) and Holtan et al., (1975a) for the last 30 days of equine pregnancy. They reported an increase in progestin levels by 5 days prepartum and a subsequent decline to less than .5 ng/ml by day 1 postpartum. However, in a similar study, Noden et al. (1975) reported that blood progesterone levels averaged 24 ng/ml 2 days before parturition and decreased to 3.3 ng/ml on the day of foaling. Allen and Hadley (1973) and Allen and Hadley (1974) also encountered large individual variations in progesterone levels in mares during pregnancy.

The mean estrogen concentrations in the blood of mares are presented in table 2. Total estrogen levels remained essentially unchanged from day 7 through day 3 prepartum

TABLE 2. MEAN PLASMA PROGESTIN, ESTROGEN AND CORTICOID LEVELS IN THE PERIPARTURIENT MARE (TRIAL 1).[a]

Days pre- and postpartum	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
-7	10	12.3 ± 1.1	11	316.4 ± 16.7	8	81.4 ± 18.5
-6	14	10.4 ± .9	15	287.8 ± 13.3	10	105.1 ± 16.0
-5	19	10.6 ± .9	19	306.5 ± 11.4	19	112.4 ± 15.0
-4	23	11.7 ± .6	20	279.7 ± 11.0	23	97.2 ± 10.7
-3	22	13.4 ± .6	18	306.2 ± 11.4	22	85.8 ± 10.8
-2	27	12.3 ± .6	25	269.5 ± 9.5	27	99.9 ± 9.6
-1	29	9.7 ± .5	24	262.2 ± 9.6	29	110.1 ± 9.3
0	28	3.2 ± .5	27	193.4 ± 9.0	26	140.0 ± 9.8
+1	23	.9 ± .9	20	148.2 ± 11.0	23	92.6 ± 14.2
+2	13	.6 ± .9	11	133.5 ± 14.8	11	90.5 ± 17.7

[a]Least square mean plasma concentrations ± standard error adjusted for mare, time of blood collection and time by day interaction.

[b]Number of samples contributing mean values for progestin.

[c]Number of samples contributing mean values for estrogen.

[d]Number of samples contributing mean values for corticoid.

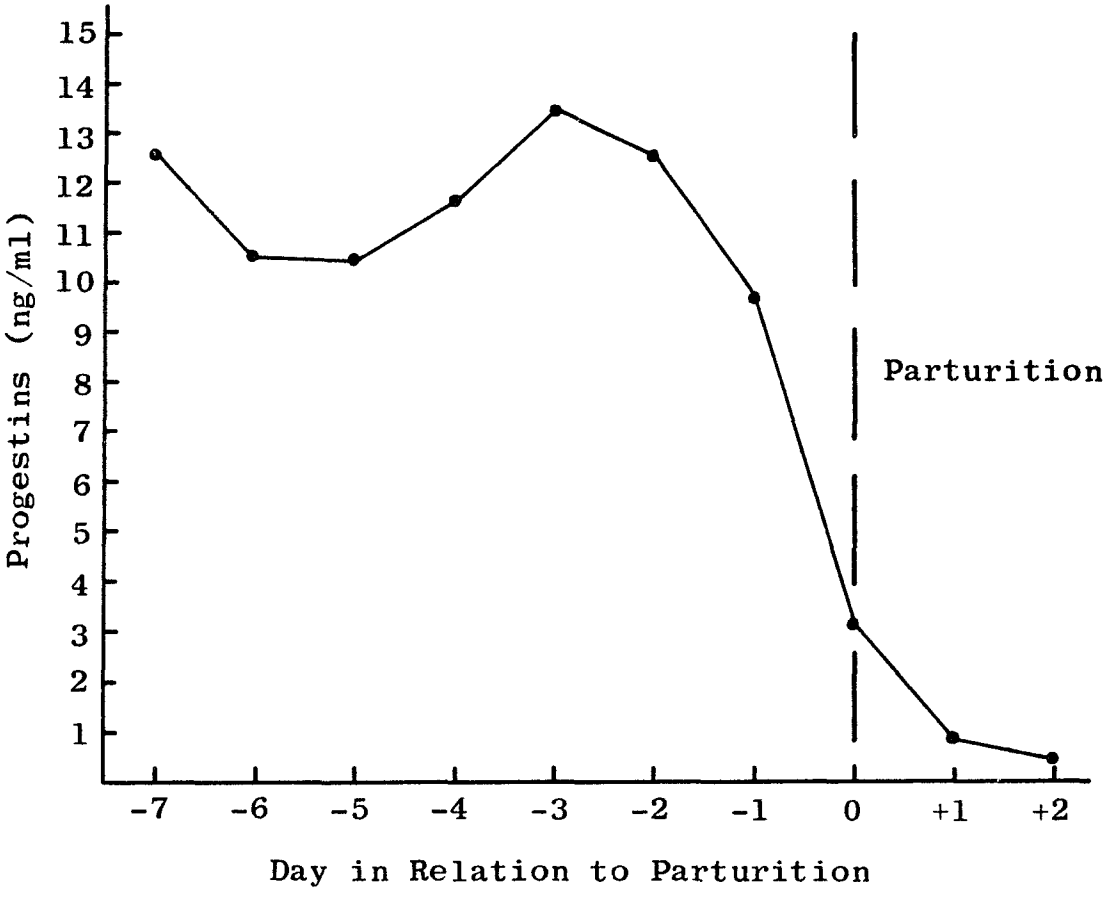

Figure 1. Mean plasma progestin concentrations in mares from day 7 prepartum through parturition to day 2 postpartum (trial 1).

TABLE 3. EFFECT OF MARE ON PLASMA PROGESTIN, ESTROGEN, AND CORTICOID LEVELS (TRIAL 1).[a]

Mare number	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
10	27	7.1 ± .6	25	268.2 ± 9.6	27	119.6 ± 9.6
11	32	8.8 ± .5	29	227.2 ± 8.8	26	156.7 ± 9.8
12	32	7.7 ± .5	29	251.2 ± 8.8	32	121.0 ± 8.7
L5	15	7.1 ± .8	17	223.4 ± 11.7	15	55.8 ± 13.3
L8	5	7.1 ± 1.4	5	240.8 ± 21.6	3	75.9 ± 29.0
17	31	12.9 ± .5	25	274.6 ± 9.5	31	75.6 ± 8.9
18	24	7.3 ± .6	20	295.6 ± 10.8	24	68.5 ± 10.2
26	18	11.8 ± .7	17	247.7 ± 11.7	16	150.9 ± 12.6
39	24	7.1 ± .6	23	224.3 ± 10.1	24	89.6 ± 10.2

[a] Least square means ± standard error adjusted for time of blood collection, day and time by day interaction.

[b] Number of samples contributing mean values for progestin.

[c] Number of samples contributing mean values for estrogen.

[d] Number of samples contributing mean values for corticoid.

(figure 2). On day 3 prior to foaling, the mean estrogen concentration was 306.2 ± 11.4 pg/ml. Concentrations then declined rather consistently to 262.2 ± 9.6 pg/ml on day 1 prepartum ($P < .01$) and continued to decline to 193.4 ± 9.0 pg/ml on the day of parturition ($P < .01$). Levels subsequently declined to 133.5 ± 14.8 pg/ml on day 2 after foaling. Estrogens were quite variable among mares ($P < .01$) with levels varying from a low of 223.4 ± 11.7 pg/ml to a high of 295.6 ± 10.8 pg/ml (table 3). A similar trend in estrogen levels was demonstrated by Nett et al. (1973) who collected blood samples from six mares at 4-day intervals from 300 days of gestation until parturition. E_1 (estrone, equilin and equilenin) levels declined steadily during the prepartum period with a precipitious drop occurring at parturition. However E_2 (estradiol) levels remained rather constant for the 30 days preceding parturition.

In contrast to decreasing progestin and estrogen concentrations mean corticoid levels increased ($P < .01$) from 85.8 ± 10.8 ng/ml on day 3 prepartum to a peak of 140.0 ± 9.8 ng/ml on the day of parturition (table 2). Levels then decreased to 90.5 ± 17.7 ng/ml on day 2 postpartum. There was considerable ($P < .01$) individual variation among mares with means ranging from 55.8 ± 13.3 to 156.7 ± 9.8 ng/ml (table 3). The pattern of increased corticoid levels at parturition (figure 3) was similar to that reported for cows (Adams and Wagner, 1970; Heitzman

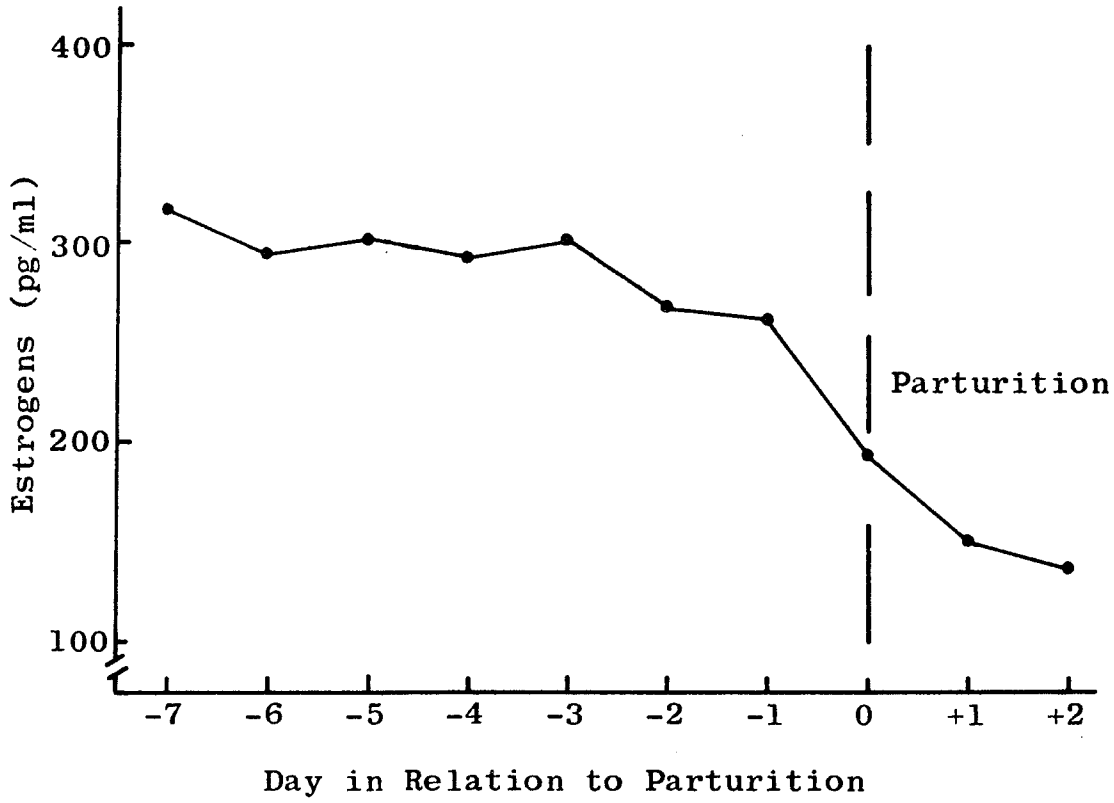

Figure 2. Mean plasma estrogen concentrations in mares from day 7 prepartum through parturition to day 2 postpartum (trial 1).

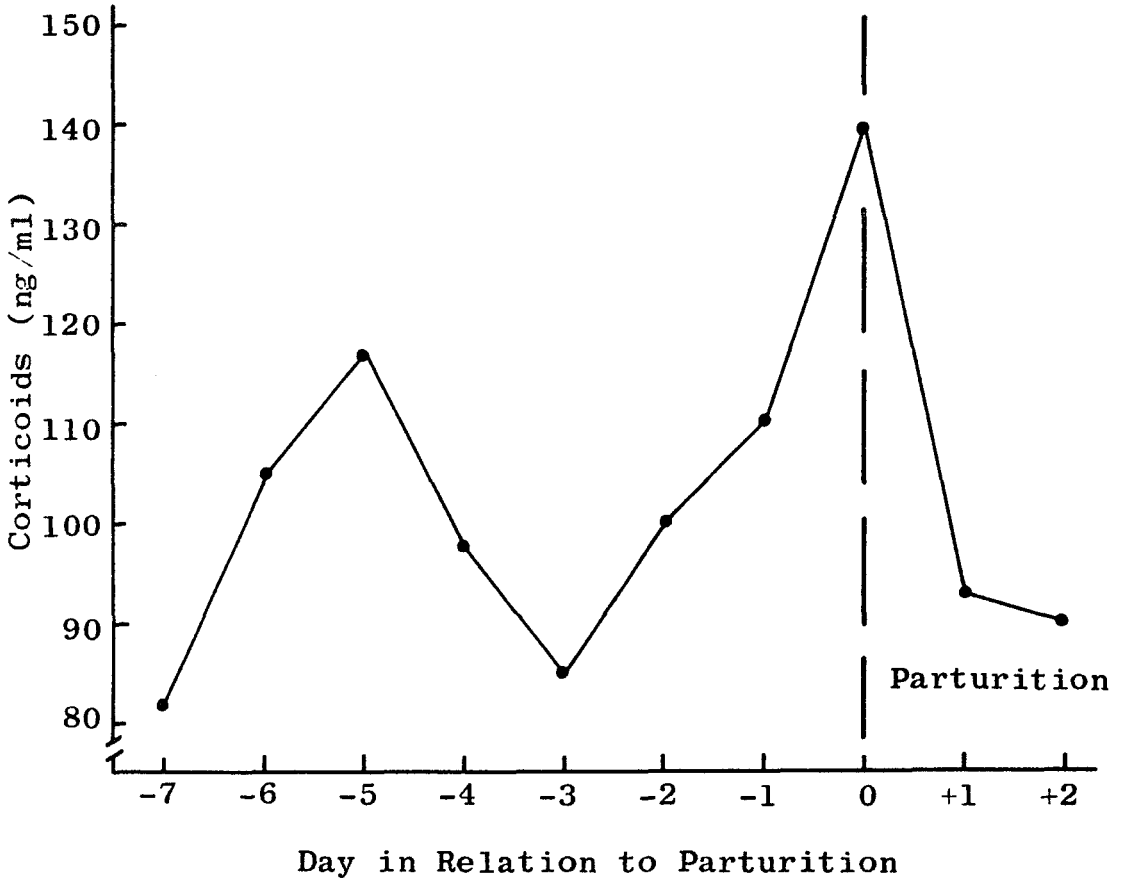

Figure 3. Mean plasma corticoid concentrations in mares from day 7 prepartum through parturition to day 2 postpartum (trial 1).

et al., 1970; Hoffmann et al., 1973; Smith et al., 1973) and sows (Killian et al., 1973; Molokwu and Wagner, 1973) except that concentrations were higher in mares. However, other researchers have reported no change in corticoid concentrations near the time of parturition in cows (Brush, 1958; Shaw et al., 1960; Garverick et al., 1974) and sows (Ash and Heap, 1975).

As illustrated in figure 4, progestin and estrogen levels declined during the final 48 hr. prior to parturition followed by a peak in corticoids at the time of foaling. A similar trend in progestin and corticoid levels was observed in swine by Molokwu and Wagner (1973) and Killian et al., (1973) who suggested that increased corticoid concentrations at birth were a result rather than an initiator of parturition.

Since previous studies have demonstrated the occurrence of a diurnal variation of some plasma steriods in other species (Wagner, 1970; MacAdam and Eberhart, 1972; Wagner and Oxenreider, 1972; Killian et al., 1973), blood samples for hormone determination were collected from mares in the morning and evening. However there was no evidence from these data of diurnal variation in blood progestin or estrogen concentrations in the pre- and postpartum mare (figure 5). Mean progestin concentrations were $8.3 \pm .4$, $8.6 \pm .6$, $8.6 \pm .4$ and $8.6 \pm .6$ ng/ml for 0600, 1200, 1800 and 2400 hr., respectively (table 4). Estrogen values

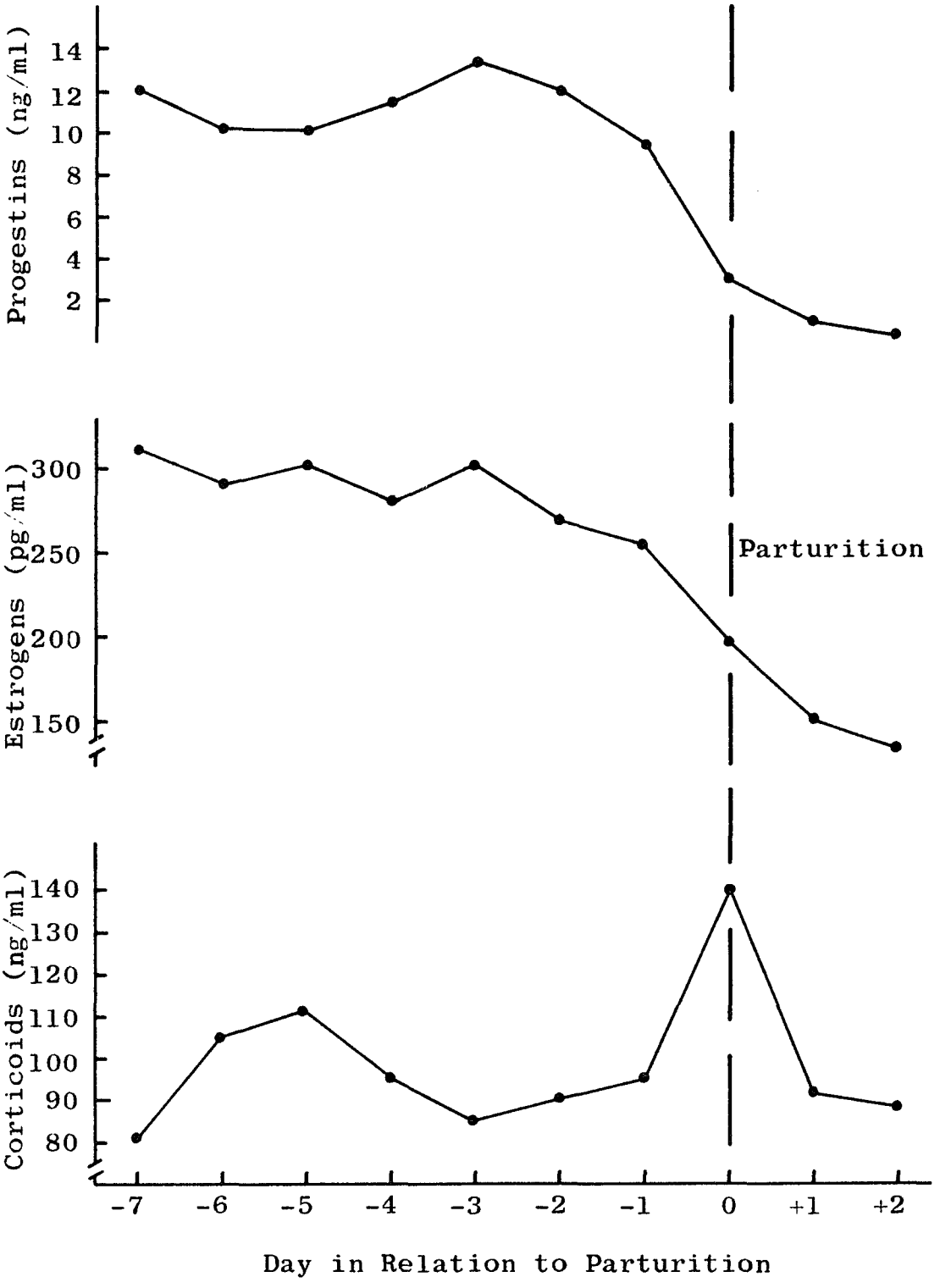

Figure 4. Mean plasma progestin, estrogen and corticoid concentrations in mares from day 7 prepartum through parturition to day 2 postpartum (trial 1).

TABLE 4. MEAN PLASMA PROGESTIN, ESTROGEN AND CORTICOID CONCENTRATIONS IN MARES AT DIFFERENT COLLECTION TIMES (TRIAL 1).[a]

Time of blood collection (hr.)	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
0600	66	8.3 ± .4	60	245.9 ± 6.2	62	108.5 ± 7.1
1200	39	8.6 ± .6	35	244.7 ± 8.9	38	115.9 ± 10.0
1800	63	8.6 ± .4	62	259.5 ± 6.3	59	88.9 ± 8.1
2400	40	8.6 ± .6	33	251.2 ± 9.8	39	92.8 ± 10.1

[a]Least square means ± standard error adjusted for mare, day and time by day interaction.

[b]Number of samples contributing mean values for progestin.

[c]Number of samples contributing mean values for estrogen.

[d]Number of samples contributing mean values for corticoid.

averaged 245.9 ± 6.2, 244.7 ± 8.9, 259.5 ± 6.3 and 251.2 ± 9.8 pg/ml for 0600, 1200, 1800 and 2400 hr., respectively (table 4).

In contrast morning samples tended to have a higher corticoid concentration than evening samples (figure 5). Mean 0600 and 1200 hr. corticoid levels were 108.5 ± 7.1 and 115.9 ± 10.0 ng/ml compared with 88.9 ± 8.1 and 92.8 ± 10.1 ng/ml for the 1800 and 2400 hr. collected samples (table 4). A similar diurnal variation in plasma corticoid levels has been reported in cows (Wagner, 1970; MacAdam and Eberhart, 1972; Wagner and Oxenreider, 1972), sows (Killian et al., 1973) geldings (Zolovick et al., 1966) and in non-pregnant mares (Hoffis et al., 1970; Bottoms et al., 1972).

The literature is devoid of information concerning the endocrine status of the newborn foal except for the early progesterone study of Short (1959) on only three foals. Since such information may be helpful in determining the etiology of equine abortion, neonate blood for hormone determination was taken by venipuncture from nine foals (five colts and four fillies) within 3 hr. of birth and on six foals (three colts and three fillies) at 24 hr. postpartum (table 5). The mean plasma progestin concentrations in the newborn foals decreased ($P < .05$) from 16.4 ± 1.9 ng/ml at birth to 5.6 ± 2.6 ng/ml 24 hr. postpartum (figure 6). A similar decline in plasma progestin levels was observed in neonate pigs by 24 and 48 hr. after farrowing (Godke and Day, 1972). Short (1959) reported that progesterone concentrations

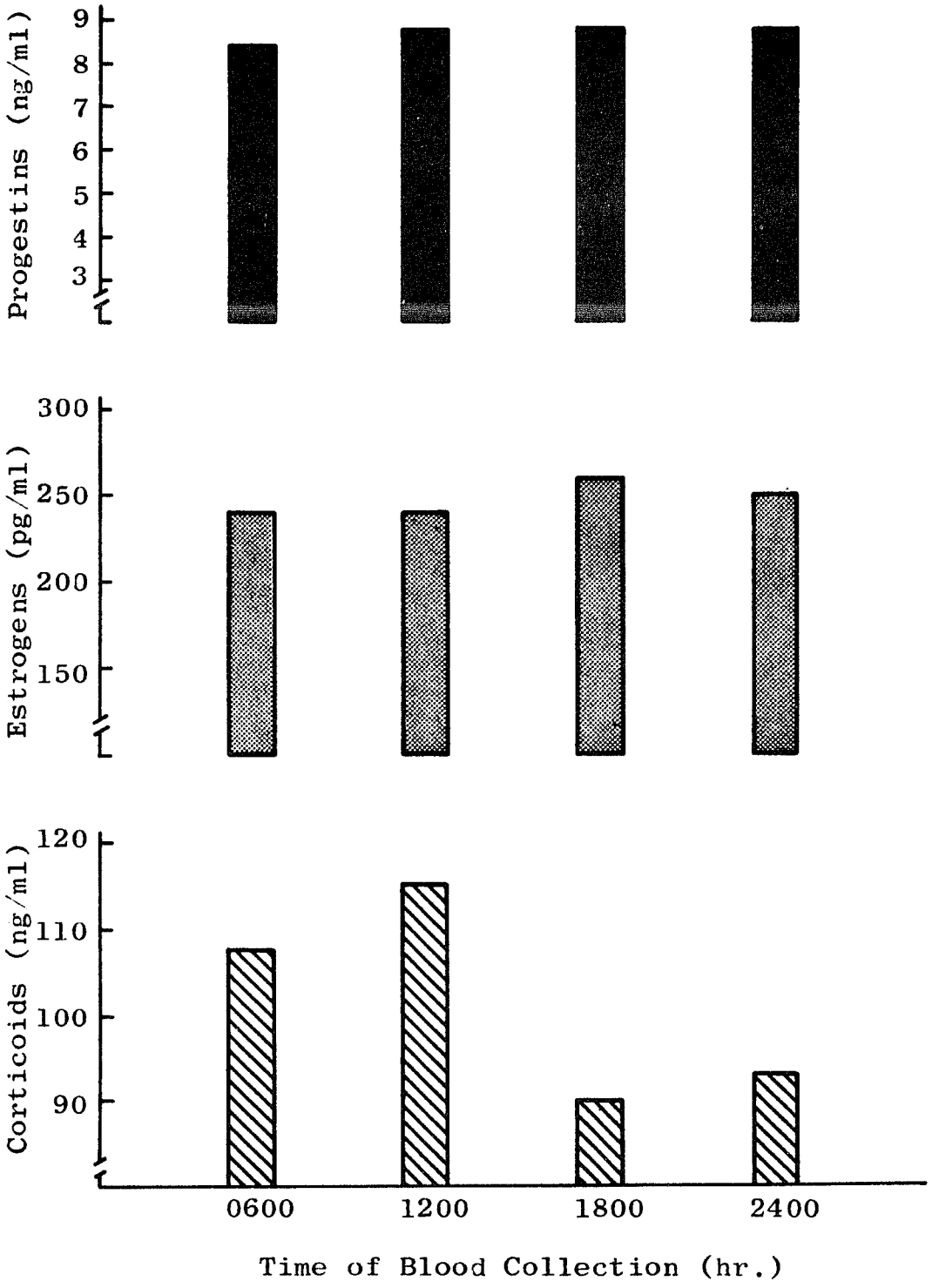

Figure 5. Mean plasma progestin, estrogen and corticoid concentrations in mares at different collection times (trial 1).

TABLE 5. MEAN PROGESTIN, ESTROGEN AND CORTICOID CONCENTRATIONS IN THE PERIPHERAL PLASMA OF FOALS AT BIRTH AND ON DAY 1 POSTPARTUM (TRIAL 1).[a]

Day in relation to foaling	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
0	9	16.4 ± 1.9*	5	171.4 ± 5.9	9	114.3 ± 8.7*
+1	6	5.6 ± 2.6	4	167.9 ± 5.0	6	69.4 ± 12.2

[a]Least square means ± standard error adjusted for foal, day and sex by day interaction.

[b]Number of samples contributing mean values for progestin.

[c]Number of samples contributing mean values for estrogen.

[d]Number of samples contributing mean values for corticoid.

*Significantly higher ($P < .05$) than levels on day 1 postpartum.

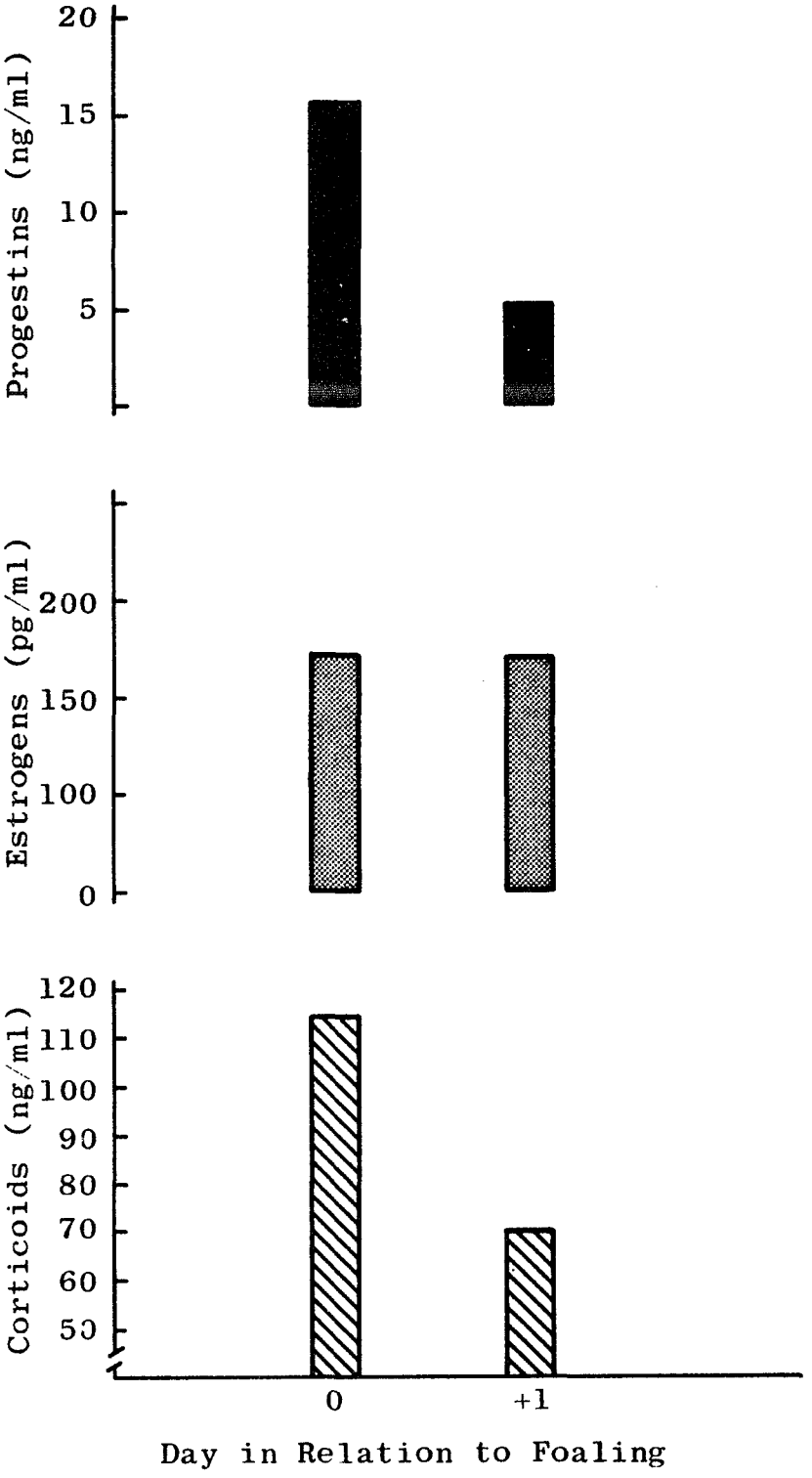

Figure 6. Mean progestin, estrogen and corticoid concentrations in the peripheral plasma of foals at the time of birth and 24 hr. postpartum (trial 1).

were high in unbilical cord blood from three foals when compared to mares at parturition. In the present study, plasma progestin levels in foals were approximately five times greater than in the peripheral blood of the mare on the day of parturition. There was no difference (table 6) in mean progestin concentrations between newborn colts (11.3 $\pm$ 2.3 ng/ml) and fillies (10.8 $\pm$ 2.3 ng/ml).

In contrast to progestin levels mean estrogen values (figure 6) in the newborn foals were similar at foaling (171.4 $\pm$ 5.9 pg/ml) and 24 hr. later (167.9 $\pm$ 5.0 pg/ml). However, newborn fillies (table 6) had a higher ($P < .05$) plasma estrogen concentration (183.2 $\pm$ 4.5 pg/ml) than the newborn colts (156.0 $\pm$ 6.4 pg/ml).

Corticoid levels in the newborn foals dropped ($P < .05$) sharply from 114.3 $\pm$ 8.7 ng/ml at parturition to 69.4 $\pm$ 12.2 ng/ml 24 hr. postpartum (figure 6). This decline in plasma corticoids subsequent to birth possibly reflects a recovery from the stress of foaling. There was no difference in mean corticoid levels (table 6) in the peripheral plasma between the newborn colts (79.6 $\pm$ 10.6 ng/ml) and fillies (104.1 $\pm$ 10.6 ng/ml).

Trial 2. A relatively small number of mares was available for the 1974 trial, therefore the study was repeated in 1975. Although steroid concentrations in the initial trial were not significantly different among the four times of blood collection, plasma corticoid levels

TABLE 6. EFFECT OF SEX ON MEAN PLASMA PROGESTIN, ESTROGEN AND CORTICOID LEVELS IN THE NEWBORN FOAL (TRIAL 1).[a]

Sex	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
Male	7	11.3 ± 2.3	3	156.0 ± 6.4	7	79.6 ± 10.6
Female	8	10.8 ± 2.3	6	183.2 ± 4.5*	8	104.1 ± 10.6

[a]Least square means ± standard error adjusted for foal, day and sex by day interaction.

[b]Number of samples contributing mean values for progestin.

[c]Number of samples contributing mean values for estrogen.

[d]Number of samples contributing mean values for corticoid.

*Significantly higher ($P < .05$) than males.

did tend to be higher in the morning collected samples than in the evening samples. Therefore blood samples in trial 2 were collected from nine mares twice daily at 0800 and 2000 hours.

The trend in plasma progestin levels in trial 2 was in close agreement with that observed in the first trial except that values were considerably lower (table 7). Levels remained between 4.5 to 5.5 ng/ml from day 7 through day 3 prepartum (figure 7). Progestin levels then dropped ($P < .01$) precipitiously from 5.3 $\pm$ .6 ng/ml on day 3 prepartum to nondetectable levels on the day of parturition and remained at near nondetectable levels through day 2 postpartum. Plasma progestin concentrations in trial 2 were different ($P < .01$) among mares. Mean levels of the hormone varied from a minimum of 1.5 $\pm$ .5 ng/ml for mare 152 to a maximum of 8.5 $\pm$ .5 ng/ml for animal 81 (table 8). The trends in progestin levels in this study are similar to those recently reported by Smith (1974) and Holtan et al. (1975a) which showed that levels of this steroid increased to 4.4 ng/ml at 5 days prepartum then declined to less than .5 ng/ml by day 1 postpartum. The relatively low plasma progestin levels observed in trial 2 were possibly due to the fact that the samples were assayed at different times and different laboratory technicians assisted in the assay. Also, different mares were used in the two trials.

TABLE 7. MEAN PLASMA PROGESTIN, ESTROGEN AND CORTICOID LEVELS IN THE PERIPARTURIENT MARES (TRIAL 2).[a]

Days pre- and postpartum	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
-7	14	5.1 ± .6	13	334.3 ± 15.3	13	52.5 ± 9.0
-6	13	4.4 ± .6	13	330.8 ± 15.3	13	84.8 ± 9.0
-5	12	4.7 ± .6	13	351.2 ± 15.2	12	89.4 ± 9.3
-4	16	5.1 ± .5	16	310.6 ± 13.7	16	87.2 ± 8.0
-3	14	5.3 ± .6	15	360.9 ± 14.2	14	78.4 ± 8.6
-2	14	5.0 ± .6	15	330.5 ± 14.2	14	89.8 ± 8.7
-1	15	3.4 ± .5	15	313.6 ± 14.0	15	93.5 ± 8.2
0	18	0.0 ± .5	18	198.8 ± 12.7	18	77.9 ± 7.4
+1	16	0.3 ± .5	16	193.9 ± 13.5	16	73.7 ± 7.9
+2	15	0.1 ± .5	14	213.9 ± 14.5	14	57.4 ± 8.6

[a] Least square means ± standard error adusted for mare, time of blood collection and time by day interaction.

[b] Number of samples contributing mean values for progestin.

[c] Number of samples contributing mean values for estrogen.

[d] Number of samples contributing mean values for corticoid.

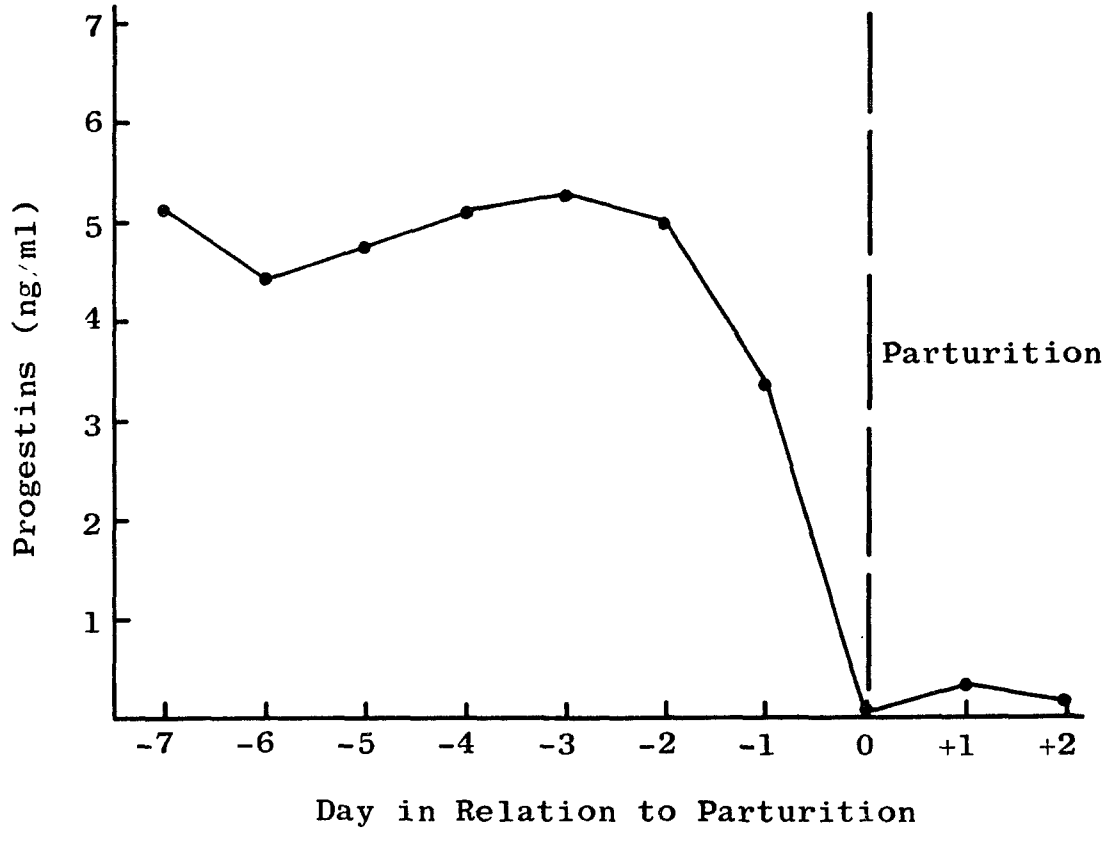

Figure 7. Mean plasma progestin concentrations in mares from day 7 prepartum through parturition to day 2 postpartum (trial 2).

TABLE 8. EFFECT OF MARE ON PLASMA PROGESTIN, ESTROGEN AND CORTICOID LEVELS (TRIAL 2).[a]

Mare number	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
12	17	2.5 ± .5	17	332.7 ± 13.2	17	111.0 ± 7.7
16	14	2.1 ± .6	15	317.4 ± 14.1	14	79.9 ± 8.6
37	19	1.8 ± .5	19	303.3 ± 12.4	19	87.8 ± 7.3
39	20	4.1 ± .5	19	275.9 ± 12.4	20	101.2 ± 7.1
41	6	3.5 ± .9	6	283.8 ± 23.0	6	80.5 ± 13.5
81	19	8.5 ± .5	18	300.7 ± 12.7	18	67.1 ± 7.5
112	16	3.1 ± .5	16	295.6 ± 13.6	16	75.2 ± 8.0
152	17	1.5 ± .5	18	293.2 ± 12.7	17	62.5 ± 7.7
162	19	2.9 ± .5	20	242.0 ± 12.0	18	41.0 ± 7.5

[a]Least square means ± standard error adjusted for time of blood collection, day and time by day interaction.

[b]Number of samples contributing mean values for progestin.

[c]Number of samples contributing mean values for estrogen.

[d]Number of samples contributing mean values for corticoid.

The concentration of total plasma estrogens followed a pattern similar to that described in trial 1 with levels fluctuating between 310 and 360 pg/ml from day 7 through day 3 prepartum (table 7). There was a trend (figure 8) toward decreasing ($P<.01$) estrogen levels beginning on day 3 (360.9 ± 14.2 pg/ml) prior to foaling and continuing through the day of foaling (198.8 ± 12.7 pg/ml). Levels further declined to 193.9 ± 13.5 pg/ml on day 1 postpartum but increased slightly on day 2 after foaling (213.9 ± 14.5 pg/ml). Similar trends in estrogen levels were reported by Nett et al. (1975) during the 30 days preceding equine parturition.

The changes in corticoid levels from day 7 through day 1 prepartum in trial 2 were in general agreement with those reported in trial 1 except that concentrations were lower (table 7). Mean corticoid levels increased from 52.5 ± 9.0 ng/ml on day 7 prior to foaling to 84.8 ± 9.0 ng/ml on day 6 prepartum (figure 9). Levels then varied between 78.4 ± 8.6 ng/ml and 93.5 ± 8.2 ng/ml until the day before parturition. However, in contrast to the sharp increase in corticoid levels observed on the day of parturition in the first trial, levels in trial 2 decreased on the day of foaling (77.9 ± 7.4 ng/ml) and continued to decline through day 2 postpartum (57.4 ± 8.6 ng/ml). This discrepancy in corticoid levels on the day of parturition may be due to the fact that blood samples in trial 1 were collected four times daily (0600, 1200, 1800 and 2400 hr.) whereas in the

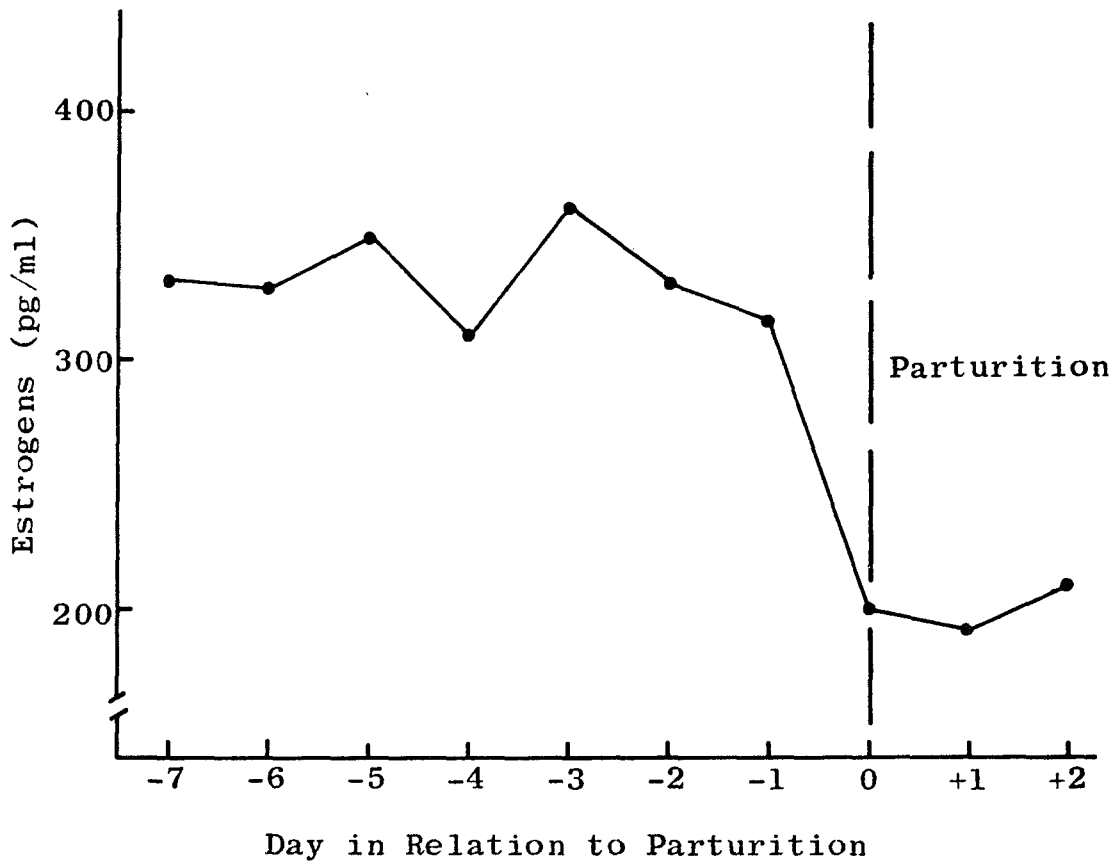

Figure 8. Mean plasma estrogen concentrations in mares from day 7 prepartum through parturition to day 2 postpartum (trial 2).

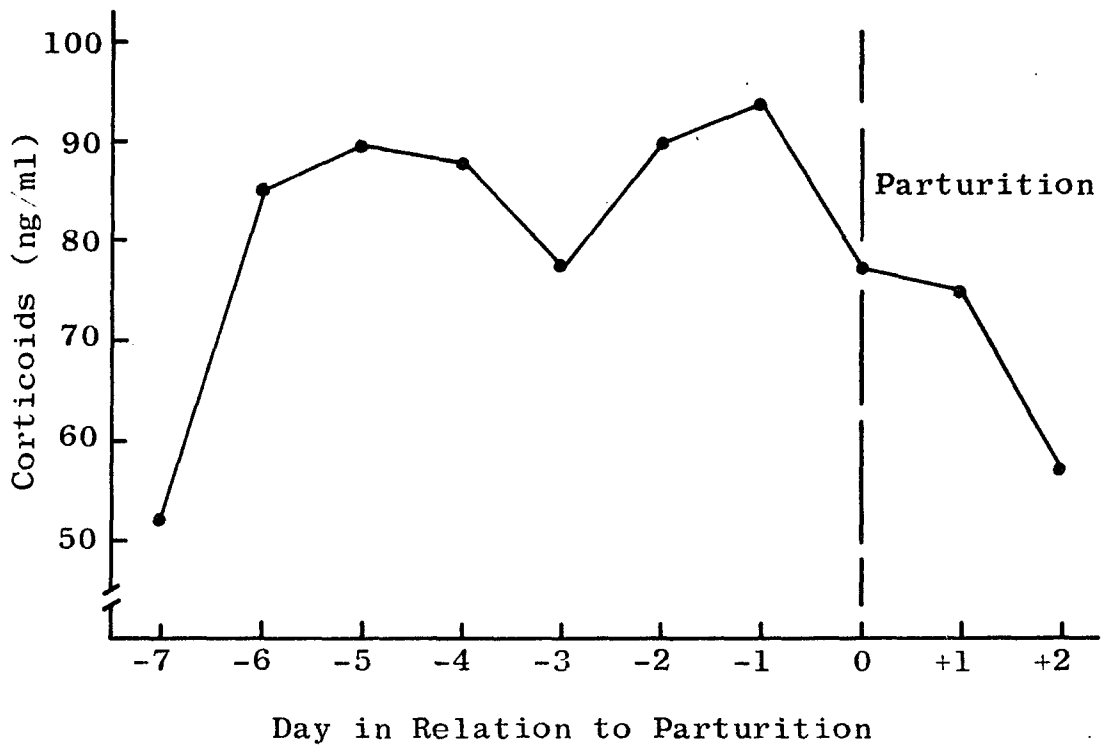

Figure 9. Mean plasma corticoid concentrations in mares from day 7 prepartum through parturition to day 2 postpartum (trial 2).

second trial, samples for hormone determination were collected twice daily (0800 and 2000 hr.). Therefore peaks in corticoid concentrations near the time of foaling may have been missed in trial 2. It is also possible that mares in trial 2 encountered less stress during foaling than those of the previous year, but this seems unlikely.

Although no studies have been conducted on corticoid levels in the periparturient mare, results from bovine and porcine studies suggest that there is a high degree of variability in corticoid concentrations at the time of parturition. Adams and Wagner (1970), Heitzman et al. (1970) and Hoffmann et al. (1973) observed a significant rise in corticoid levels near the time of parturition in cattle, while Brush (1958), Shaw et al. (1960) and Garverick et al. (1974) found no particular pattern in the levels of this compound in periparturient cows. In the sow, Killian et al. (1973) and Molokwu and Wagner (1973) reported a peak in corticoid levels on the day of farrowing, but Ash and Heap (1975) observed no consistent change at the time of parturition in this species.

A comparison of mean steroid hormone levels in the blood of trial 1 and 2 mares (figure 10) revealed that plasma progestin and estrogen concentrations followed a similar pattern in both trials with levels dropping precipitiously during the final 48 hr. preceeding parturition. However mean corticoid levels peaked on the day of foaling in trial 1 and declined during this same period in trial 2

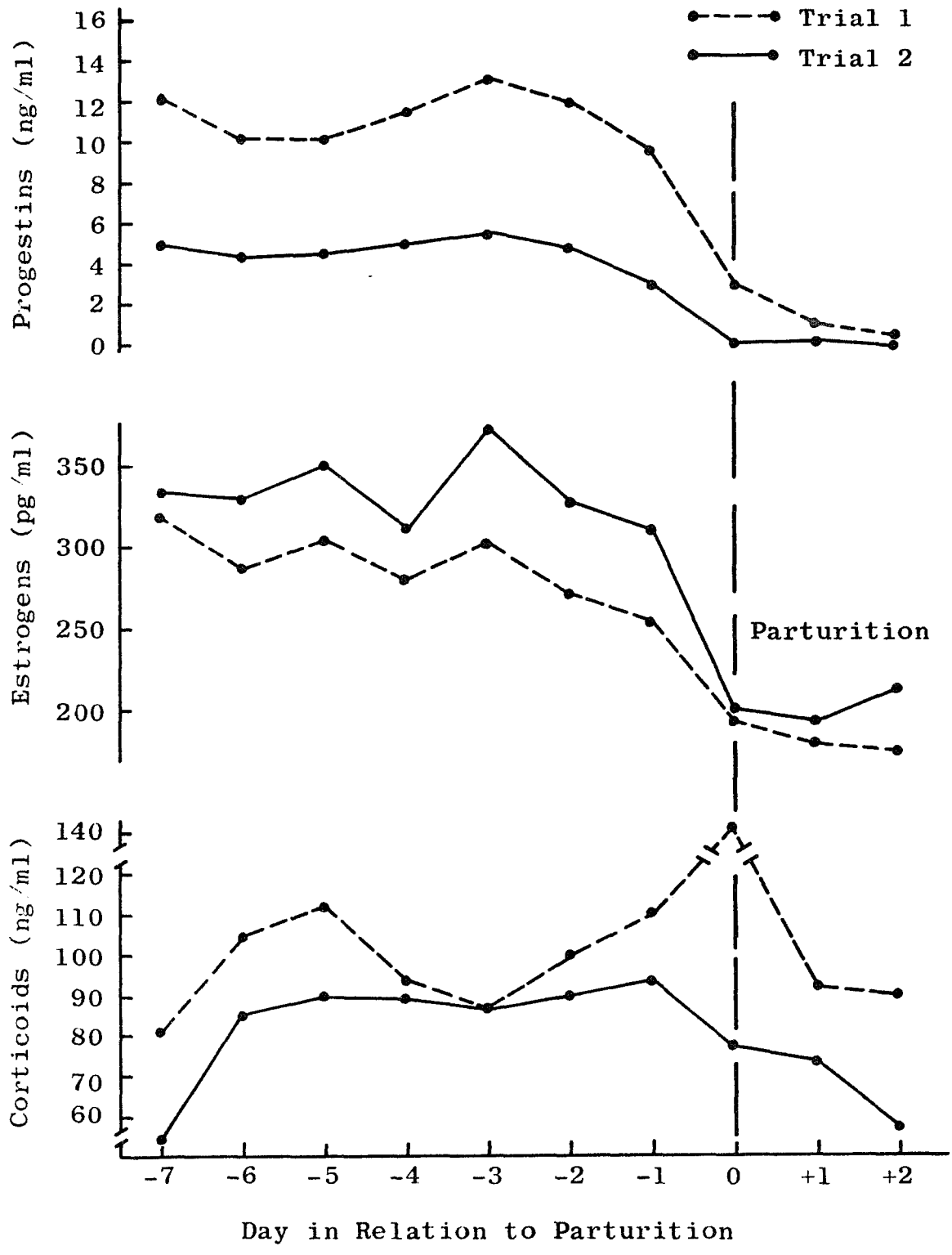

Figure 10. Mean plasma progestin, estrogen and corticoid concentrations in mares from day 7 prepartum through parturition to day 2 postpartum (trial 2). Trial 1 values are included for comparison.

mares. The trend in progestin and estrogen levels for the periparturient mares in trial 2 compares favorably with the results of Nett et al. (1973), Smith (1974) and Holtan et al. (1975a). Differences in corticoid concentration on the day of foaling in the two trials may have been due to the frequency of blood sample collections and to stress factors already discussed.

No significant diurnal variation in hormone levels was detected among the four sampling periods in trial 1. However in view of the diurnal trends in corticoid levels observed in the initial trial, blood samples for hormone determination in trial 2 were collected twice daily at 0800 and 2000 hours. Statistical analysis of trial 2 data revealed a significant diurnal variation in corticoid levels in the pre- and postpartum mare (table 9). The mean 0800 hr. level was 90.7 $\pm$ 3.4 ng/ml compared to 66.2 $\pm$ 3.9 ng/ml for the 2000 hr. collected samples (figure 11). Similar to the results of the initial trial, plasma progestin and estrogen concentrations in trial 2 showed no diurnal variation (table 9). Mean progestin levels were 3.4 $\pm$ .2 ng/ml at 0800 hr. and 3.4 $\pm$ .2 ng/ml at 2000 hr., while mean estrogen concentrations were 301.6 $\pm$ 6.6 and 286.1 $\pm$ 6.4 pg/ml for 0800 and 2000 hr., respectively (figure 11).

In order to monitor steriod levels in the newborn foals, neonate blood was taken from four colts and five fillies by venipuncture within 6 hr. of birth and 24 and 48 hr. postpartum (table 10). Mean plasma progestin concentrations

TABLE 9. MEAN PLASMA PROGESTIN, ESTROGEN AND CORTICOID CONCENTRATIONS IN MARES AT DIFFERENT COLLECTION TIMES (TRIAL 2).[a]

Time of blood collection (hr.)	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
0800	74	3.4 ± .2	72	301.6 ± 6.6	74	90.7 ± 3.4**
2000	73	3.4 ± .2	76	286.1 ± 6.4	71	66.2 ± 3.9

[a]Least square means ± standard error adjusted for mare, day and time by day interaction.

[b]Number of samples contributing mean values for progestin.

[c]Number of samples contributing mean values for estrogen.

[d]Number of samples contributing mean values for corticoid.

**Significantly higher ($P < .01$) than 2000 hr. collected blood samples.

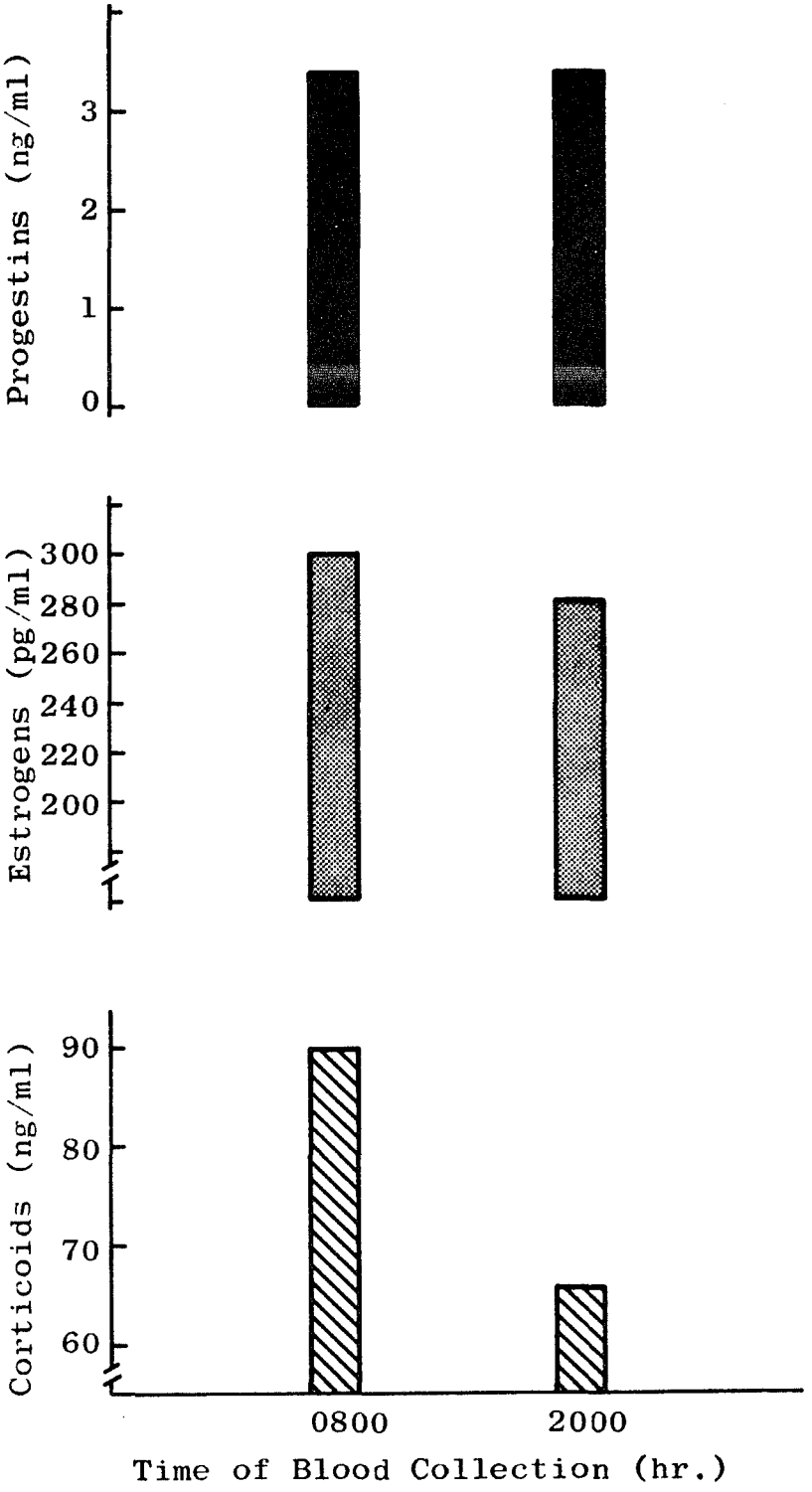

Figure 11. Mean plasma progestin, estrogen and corticoid concentrations in mares at different collection times (trial 2).

TABLE 10. MEAN PROGESTIN, ESTROGEN AND CORTICOID CONCENTRATIONS IN THE PERIPHERAL PLASMA OF FOALS AT BIRTH AND AT 24 AND 48 HR. POSTPARTUM (TRIAL 2).[a]

Day in relation to foaling	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
0	8	2.6 ± .5**	8	188.9 ± 17.4	8	59.7 ± 16.6
+1	7	0.8 ± .6	8	173.4 ± 16.6	7	35.8 ± 18.4
+2	8	0.3 ± .5	8	177.2 ± 17.4	8	7.4 ± 17.0

[a]Least square means ± standard error adjusted for foal, sex and sex by day interaction.

[b]Number of samples contributing mean values for progestin.

[c]Number of samples contributing mean values for estrogen.

[d]Number of samples contributing mean values for corticoid.

** Significantly higher ($P < .01$) than levels at 24 and 48 hr. postpartum.

decreased ($P < .01$) from 2.6 $\pm$ .5 ng/ml at birth to .8 $\pm$ .6 ng/ml 24 hr. later and further declined to .3 $\pm$ .5 ng/ml at 48 hr. postpartum (figure 12). Progestin levels on the 2 days postpartum were not significantly different. These findings are in agreement with those reported for the first trial except that hormone values were lower than in the previous year. As previously stated, this discrepancy may be due to time of assay, animal and technician differences. Sex of the foal appeared to have no effect on progestin levels since males had a mean progestin concentration of 1.6 $\pm$ .5 ng/ml compared to 0.9 $\pm$ .4 ng/ml for the females (table 11).

Plasma estrogen levels in the newborn foals remained fairly stable during the period of blood sample collections (figure 12). Mean estrogen values were 188.9 $\pm$ 17.4 pg/ml on the day of parturition, 173.4 $\pm$ 16.6 pg/ml on day 1 and 177.2 $\pm$ 17.4 pg/ml on day 2 after foaling (table 10). These values are in close agreement with those reported in the initial trial. In contrast to the results of trial 1 sex of the foal had no effect on mean estrogen values in the present trial. Mean estrogen levels were 188.4 $\pm$ 12.5 and 171.2 $\pm$ 15.0 pg/ml for colts and fillies, respectively (table 11).

Circulating corticoid levels in the newborn foals decreased from 59.7 $\pm$ 16.6 ng/ml at birth to 35.8 $\pm$ 18.4 ng/ml 24 hr. later and continued to decrease to 7.4 $\pm$ 17.0 ng/ml by 48 hr. postpartum (table 10 and figure 12). A similar

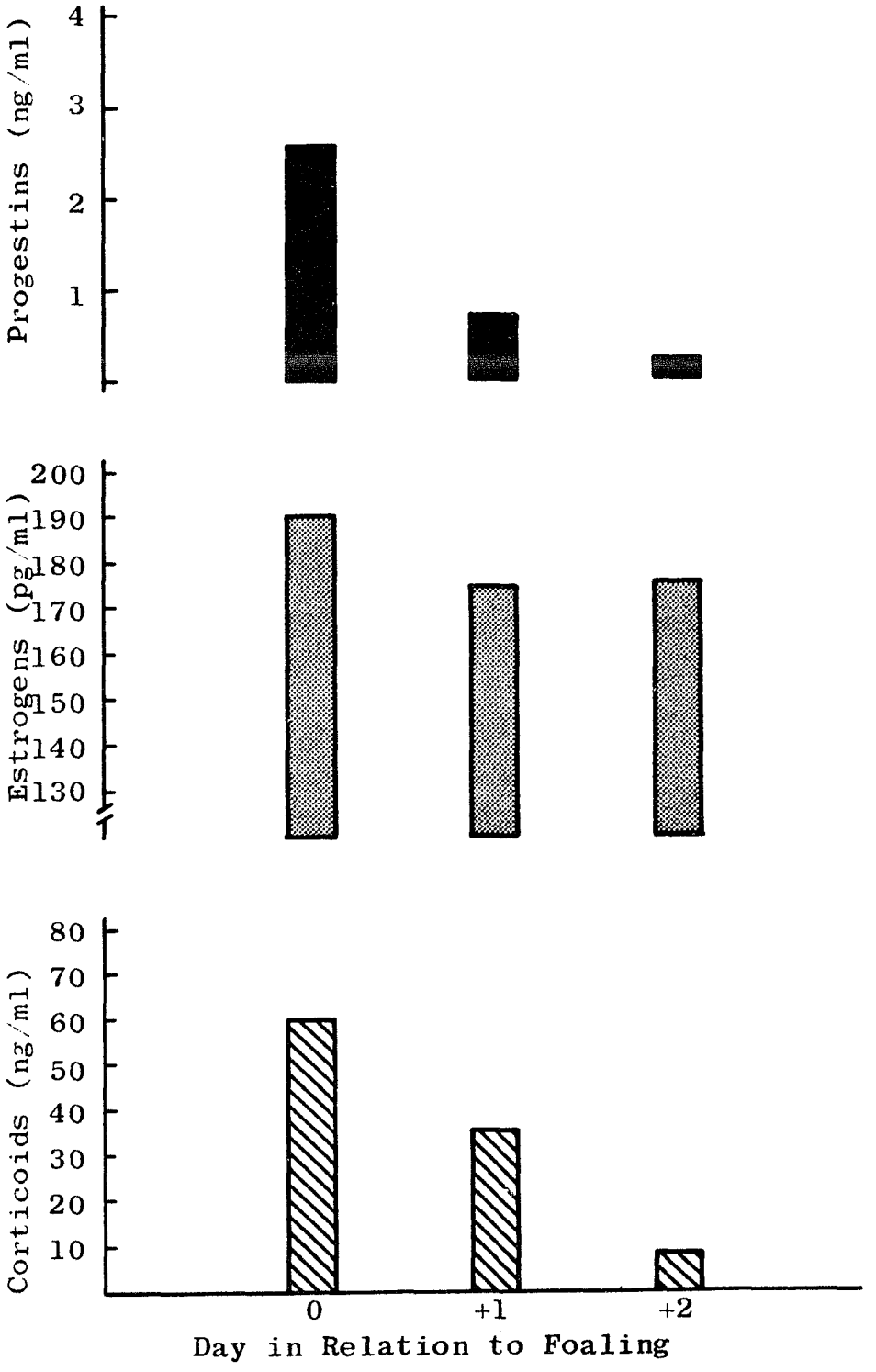

Figure 12. Mean progestin, estrogen and corticoid concentrations in the peripheral plasma of foals at the time of birth and 24 and 48 hr. postpartum (trial 2).

TABLE 11. EFFECT OF SEX ON THE MEAN PLASMA PROGESTIN, ESTROGEN AND CORTICOID LEVELS IN THE NEWBORN FOAL (TRIAL 2).[a]

Sex	n[b]	Progestin (ng/ml)	n[c]	Estrogen (pg/ml)	n[d]	Corticoid (ng/ml)
Male	12	1.6 ± .5	14	188.4 ± 12.5	12	32.0 ± 15.1
Female	11	0.9 ± .4	10	171.2 ± 15.0	11	36.6 ± 13.9

[a] Least square means ± standard error adjusted for time of blood collection, day and time by day interaction.

[b] Number of samples contributing mean values for progestin.

[c] Number of samples contributing mean values for estrogen.

[d] Number of samples contributing mean values for corticoid.

decrease in corticoid levels was observed for newborn foals in the first trial. Again there was no difference (table 11) in corticoid concentrations between colts (32.0 $\pm$ 15.1 ng/ml) and fillies (36.6 $\pm$ 13.9 ng/ml).

The results of this experiment indicate that peripheral plasma progestin and estrogen levels decline during the 48 hr. preceeding parturition and that corticoid concentrations are quite variable in the periparturient mare. Also, these data suggest that progestin and corticoid levels decline in the Quarter Horse foal during the first 48 hr. postpartum.

Experiment II. Induction of Estrus after Foal Heat with Prostaglandin $F_{2\alpha}$.

In a second study two trials were conducted to determine if prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) could be used to induce estrus in mares shortly after foal heat and thus reduce the interval from foaling to rebreeding while circumventing the undesirable effects of breeding on the first postpartum estrus.

Trial 1. In the initial trial 14 Quarter Horse mares ranging in age from 5 to 13 years were allotted to three treatment groups. On day 6 and day 7 after foal estrus, four mares were given a 10 mg subcutaneous injection (SC) of $PGF_{2\alpha}$ -free acid ($PGF_{2\alpha}$) and five mares were injected with 15 mg (SC) of $PGF_{2\alpha}$ -tham salt. Control mares were given injections of an equal volume of sterile saline.

Data on estrus and ovulation in $PGF_{2\alpha}$ treated and control mares are presented in table 12. The mean interval from foaling to the onset of foal estrus was similar for the $PGF_{2\alpha}$ (8.5 $\pm$ 1.3 days), $PGF_{2\alpha}$ - tham salt (10.4 $\pm$ 1.1 days) and control (7.2 $\pm$ 1.1 days) mares. These values are in agreement with those reported by Constantinescu and Mauch (1938) and Trum (1950) who studied over a thousand foalings of light mares. The interval between the initial injection and the onset of estrus for the present study was shorter ($P < .01$) in the $PGF_{2\alpha}$ and $PGF_{2\alpha}$ - tham salt treated mares (5.0 $\pm$ 2.7 and 5.0 $\pm$ 2.5 days, respectively) than in the control females (17.0 $\pm$ 2.5 days). Although linear contrasts revealed a difference ($P < .01$) in the interval from the initial injection to the onset of estrus between treated and control mares (control vs $PGF_{2\alpha}$, $PGF_{2\alpha}$ - tham salt), there was no difference between the two PGF_2 treatment groups ($PGF_{2\alpha}$ vs $PGF_{2\alpha}$ - tham salt). Douglas and Ginther (1972), Allen and Rowson (1973), Noden et al., (1974), Thompson and Witherspoon (1974) and Douglas and Ginther (1975a,b) reported that cycling mares returned to estrus 1.5 to 5 days following treatment with $PGF_{2\alpha}$. Tolksdorff (1975) and Witherspoon et al. (1975) observed that most lactating postpartum mares showed estrus 5 days after injections of the $PGF_{2\alpha}$ analogue RS9390.

All treated and control mares ovulated on the second estrus after foaling with mean time intervals from injection

TABLE 12. ESTRUS AND OVULATION IN PROSTAGLANDIN $F_{2\alpha}$ TREATED AND CONTROL MARES (TRIAL 1).

Interval between:	Treated (days)		Control (days)
	$PGF_{2\alpha}$ - free acid[a]	$PGF_{2\alpha}$ - tham salt[b]	Saline[c]
Parturition and foal heat	8.5 ± 1.3[d]	10.4 ± 1.1	7.2 ± 1.1
First injection and estrus	5.0 ± 2.7**	5.0 ± 2.5**	17.0 ± 2.5
First injection and ovulation	9.0 ± 3.2*	10.2 ± 2.8*	21.8 ± 2.8
Onset of 2nd estrus and ovulation	4.0 ± 1.0	5.2 ± .9	4.8 ± .9
Ovulation and end of 2nd estrus	1.0 ± .2	1.2 ± .2	1.0 ± .2
Foal heat and 2nd estrus	11.0 ± 2.7**	11.4 ± 2.5**	24.8 ± 2.5
Foaling and 2nd estrus	23.0 ± 2.3**	24.6 ± 2.1**	34.2 ± 2.1
Foaling and 2nd estrus ovulation	27.0 ± 2.7**	29.2 ± 2.4**	39.0 ± 2.4

[a] Administered 10 mg (SC) injection of $PGF_{2\alpha}$ -free acid on days 6 and 7 after end of foal heat (4 mares).

[b] Administered 15 mg (SC) injection of $PGF_{2\alpha}$ -tham salt on days 6 and 7 after end of foal heat (5 mares).

[c] Administered 1.5 ml sterile saline on days 6 and 7 after end of foal heat (5 mares).

[d] Least square mean ± standard error.

* Significantly shorter ($P < .05$) than controls.

** Significantly shorter ($P < .01$) than controls.

to ovulation of 9.0 ± 3.2 and 10.2 ± 2.8 days for the $PGF_{2\alpha}$ and $PGF_{2\alpha}$ - tham salt treated females compared to 21.8 ± 2.8 days for the saline injected controls ($P < .05$). The mean intervals from treatment to ovulation of treated mares in the present study agree with the results of Noden et al. (1974), Douglas and Ginther (1975a) and Miller et al. (1976) who reported that mares ovulated 8 to 11.5 days following $PGF_{2\alpha}$ treatment.

Ovulation in the present study occurred on the average 4.0 ± 1.0 days and 5.2 ± .9 days after the onset of second estrus in $PGF_{2\alpha}$ and $PGF_{2\alpha}$ - tham salt treated mares compared to 4.8 ± .9 days for controls. In contrast Noden et al. (1974) reported that the interval from onset of estrus to ovulation was longer after $PGF_{2\alpha}$ was given to cycling mares. Treatment of mares with $PGF_{2\alpha}$ or $PGF_{2\alpha}$ - tham salt in the present trial did not alter the interval from ovulation to end of estrus since treated mares ovulated 1.0 ± .2 and 1.2 ± .2 days and control females 1.0 ± .2 days before the end of estrus. In a similar study Noden et al. (1975) noted that the interval from ovulation to the end of estrus was 1.6 days in $PGF_{2\alpha}$ - tham salt treated cycling nonlactating mares.

Treatment with $PGF_{2\alpha}$ (11.0 ± 2.7 days) or $PGF_{2\alpha}$ - tham salt (11.4 ± 2.5 days) shortened ($P < .01$) the interval from foal heat to the onset of second estrus (interestrual period) when compared to controls (24.8 ± 2.5 days).

However, there was no difference in the lengths of interestrual periods between the two $PGF_{2\alpha}$ treatment groups ($PGF_{2\alpha}$ vs $PGF_{2\alpha}$ - tham salt). These interestrual intervals in the $PGF_{2\alpha}$ treated mares compare favorably with the 9.4 days reported by Noden et al. (1974) after treatment of normal cycling mares with PGF_2 - tham salt.

As illustrated in figure 13, the interval between foaling and the onset of the second estrus was decreased ($P < .01$) as a result of treatment with $PGF_{2\alpha}$ (23.0 $\pm$ 2.3 days) or $PGF_{2\alpha}$ - tham salt (24.6 $\pm$ 2.1 days) as compared to saline injected control mares (34.2 $\pm$ 2.1 days). Also, the interval between foaling and second estrus ovulation was decreased ($P < .01$) in the $PGF_{2\alpha}$ treated mares (27.0 $\pm$ 2.7 days for $PGF_{2\alpha}$ and 29.2 $\pm$ 2.4 days for $PGF_{2\alpha}$ - tham salt) as compared to the controls (39.0 $\pm$ 2.4 days). Thus the time interval from foaling to rebreeding was reduced in the treated mares. The form of $PGF_{2\alpha}$ (free acid or tham salt) used however did not appear to matter since intervals from foaling to estrus and ovulation were similar for both treated groups. These results correspond well with those of Witherspoon et al. (1975) who reported that 17 of 22 mares treated with the $PGF_{2\alpha}$ analogue RS9390 conceived by the first month postpartum.

Data on duration of estrus and reproductive efficiency are presented in table 13. Foal estrus lasted 3.5 $\pm$ .8 days for $PGF_{2\alpha}$ treated mares, 2.6 $\pm$ .7 days for $PGF_{2\alpha}$ - tham

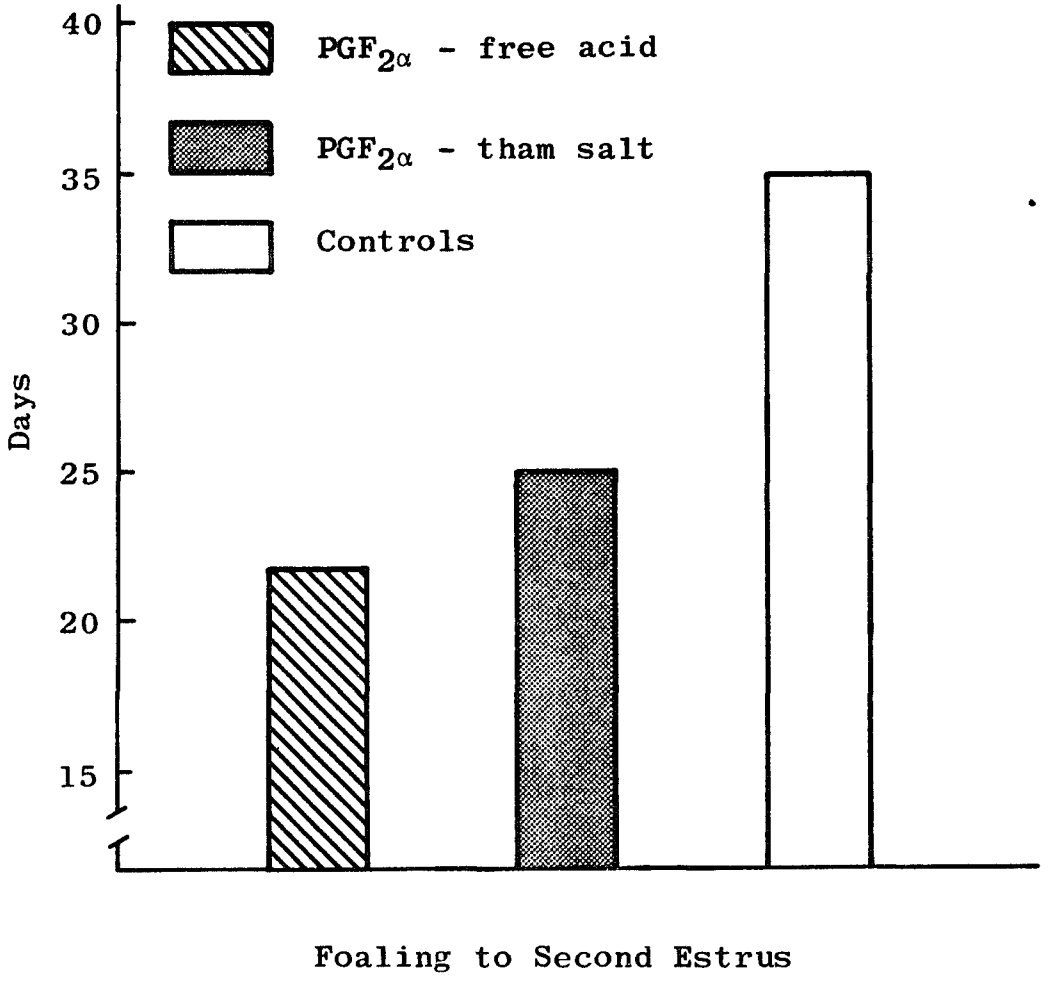

Figure 13. The time interval between foaling and the second postpartum estrus in treated and control mares (trial 1).

TABLE 13. DURATION OF ESTRUS AND REPRODUCTIVE EFFICIENCY OF PROSTAGLANDIN $F_{2\alpha}$ TREATED AND CONTROL MARES (TRIAL 1).

Item	Treated		Control
	$PGF_{2\alpha}$ - free acid[a]	$PGF_{2\alpha}$ - Tham salt[b]	Sterile Saline[c]
Duration of foal estrus, days	3.5 ± .8[d]	2.6 ± .7	3.6 ± .7
Duration of 2nd estrus, days	5.0 ± 1.0	6.4 ± .9	5.8 ± .9
Conception rate, %	100	80	100
Services per coneption, no.	2.2 ± .6	2.2 ± .5	2.4 ± .5

[a]Administered 10 mg (SC) injection of $PGF_{2\alpha}$ -free acid on days 6 and 7 after end of foal heat (4 mares).

[b]Administered 15 mg (SC) injection of $PGF_{2\alpha}$ -tham salt on days 6 and 7 after end of foal heat (5 mares).

[c]Administered 1.5 ml sterile saline on days 6 and 7 after end of foal heat (5 mares).

[d]Least square mean ± standard error.

salt treated females and 3.6 $\pm$ .7 days for controls. These results on the length of foal estrus compare favorably with those of Andrews and McKenzie (1941), Mahaffey (1950) and Arora and Luktuke (1972). Length of the second estrus postpartum was also similar for $PGF_{2\alpha}$ (5.0 $\pm$ 1.0 days), $PGF_{2\alpha}$ - tham salt (6.4 $\pm$ .9 days) and control (5.8 $\pm$ .9 days) mares. These means are within the 5 to 7 day range reported by Lieux (1963) and Nishikawa and Hafez (1968) for normal cycling mares. However, Noden et al. (1974) observed that estrus persisted longer after $PGF_{2\alpha}$ - tham salt was given to cycling mares.

Treatment of mares with $PGF_{2\alpha}$ did not appear to adversely affect fertility since all of the $PGF_{2\alpha}$ - free acid and control mares and four of five $PGF_{2\alpha}$ - tham salt treated females conceived on the second estrus after foaling. Similar conception rates were observed by Tolksdorff, 1975 (81%) and Witherspoon et al., 1975 (77%) using the $PGF_{2\alpha}$ analogue RS9390 after foal heat.

Breeding efficiency was also similar for all treatments with 2.2 $\pm$ .6, 2.2 $\pm$ .5 and 2.4 $\pm$ .5 services per conception for the $PGF_{2\alpha}$, $PGF_{2\alpha}$ - tham salt and control groups, respectively. Tolksdorff (1975) reported that 2.5 services were required per conception in mares induced with RS 9390 compared to 3.2 services for controls.

In order to confirm the luteolytic effect of $PGF_{2\alpha}$ in the mare, blood samples for progestin determination were

collected 15 min. before and after the first and second injections of $PGF_{2\alpha}$ - tham salt and daily thereafter until the onset of estrus. The effect of treatment with $PGF_{2\alpha}$ - tham salt on the mean progestin concentrations in the peripheral plasma of four mares is illustrated in figure 14. Blood progestin levels showed a slight increase (from 2.9 ± 1.7 to 3.8 ± 1.9 ng/ml) 15 min. following the first injection of $PGF_{2\alpha}$ - tham salt. Progestin levels then dropped rapidly to $.4 \pm .2$ ng/ml 15 min. after the second injection. Levels remained at less than .5 ng/ml until the onset of estrus which occurred on the average 5 days after the first $PGF_{2\alpha}$ injection. Pretreatment progestin levels in this trial were within the range reported by Tolksdorff (1975) and Witherspoon et al. (1975) for lactating postpartum mares. Also the rapid decline in progestin levels after $PGF_{2\alpha}$ treatment is similar to trends reported by Allen and Rowson (1973), Noden et al. (1974), Thompson and Witherspoon (1974) and Douglas and Ginther (1975a) in cycling mares and by Tolksdorf (1975) and Witherspoon et al. (1975) in lactating postpartum mares following the use of a $PGF_{2\alpha}$ analogue. It is significant to note however that the progestin profile of mare LI0 after $PGF_{2\alpha}$ - tham salt in the present study (figure 15) is atypical of that observed in the other treated mares. Blood progestin levels in this mare never exceeded 1.5 ng/ml during the time of blood sample collections. Peripheral progestin concentrations

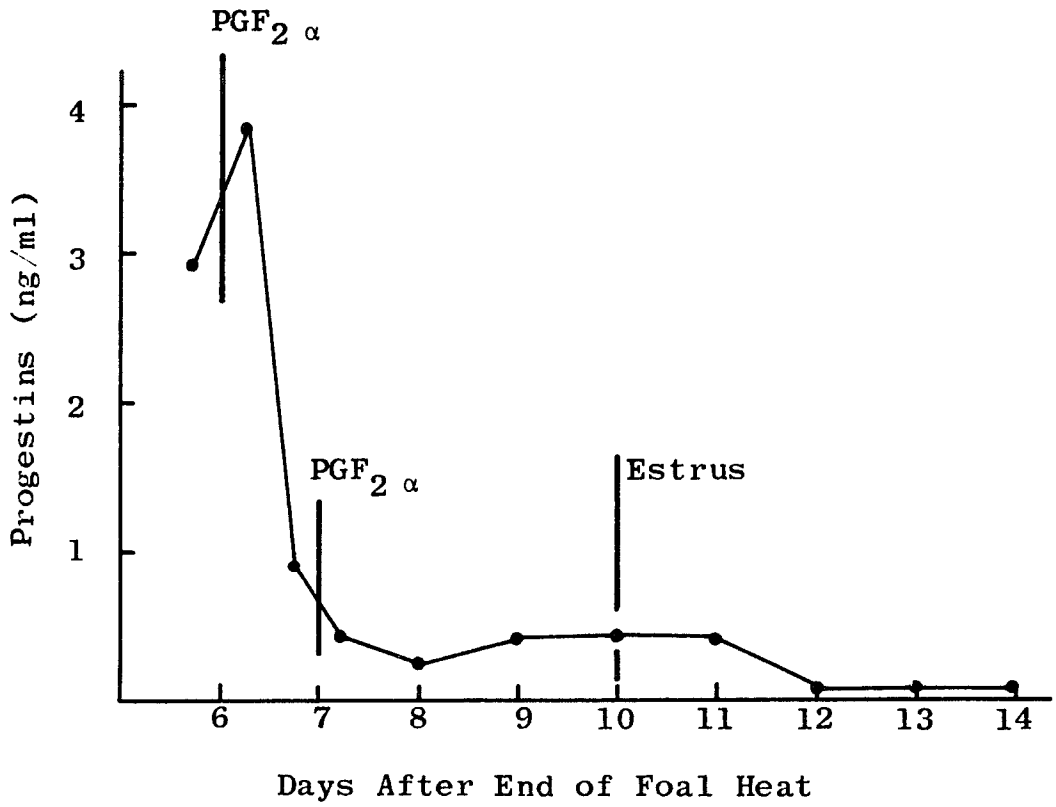

Figure 14. Mean progestin levels in the peripheral plasma of $PGF_{2\alpha}$ treated mares (trial 1).

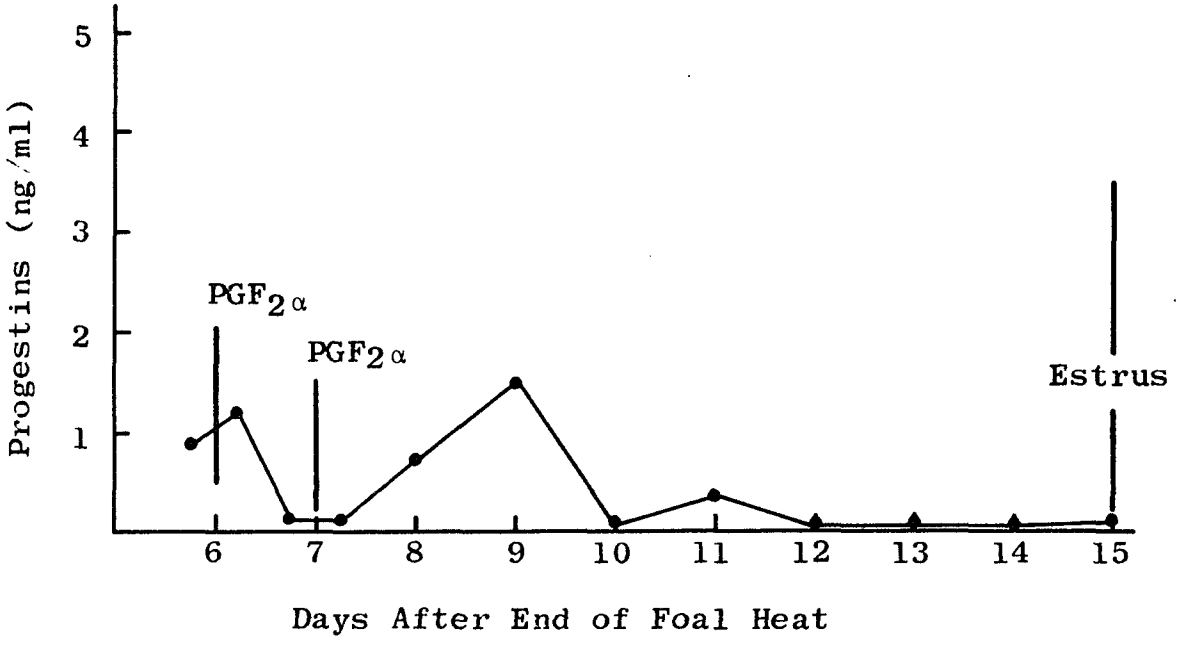

Figure 15. Progestin levels in the peripheral plasma of mare L-10 following $PGF_{2\alpha}$ treatment (trial 1).

showed a temporary decline on day 7 followed by a gradual increase to 1.5 ng/ml by day 9 after foal heat. Progestins then declined to nondetectable levels but the mare did not show signs of estrus until 10 days after the initial $PGF_{2\alpha}$ - tham salt injection. Witherspoon et al. (1975) also observed a temporary decline and recovery of luteal function in a lactating postpartum mare following treatment with a $PGF_{2\alpha}$ analogue. The precipitious decline in progestins and consistent return to estrus observed in the majority of mares in the present study suggests that $PGF_{2\alpha}$ causes luteolysis in the postpartum lactating mare.

Previous studies with mares suggested that $PGF_{2\alpha}$ and the $PGF_{2\alpha}$ analogue ICI 79939 and Prostin $F_{2\alpha}$® often caused adverse side effects in mares manifested by profuse sweating, increased respiration and cardiac rates, mild colic, watery diarrhea, reduced rectal temperature and reduced appetite (Allen and Rowson, 1973; Allen and Rossdale, 1973; Allen et al., 1974; Lauderdale et al., 1975 a,b). Although no attempt was made to critically study the side effects of PGF_2 in the present study, mares were observed for adverse reactions following injections of $PGF_{2\alpha}$ and $PGF_{2\alpha}$ - tham salt.

Profuse sweating of the head, neck, chest and lower abdominal regions of the body were recorded in mares treated with $PGF_{2\alpha}$ and $PGF_{2\alpha}$ - tham salt. Sweating started 15 to 20 min. after $PGF_{2\alpha}$ injection and ceased about 2 hr.

following treatment indicating that the effect was transitory. No other side effects were noted. A sweating response after treatment of stallions with $PGF_{2\alpha}$ was reported by Cornwell et al. (1974). In addition profuse sweating accompanied by a reduction in rectal temperature was reported by Lauderdale et al. (1975a) after the administration of 1 to 10 mg of Prostin $F_{2\alpha}$® ($PGF_{2\alpha}$) to mares. In a related study, Lauderdale et al. (1975b) suggested that $PGF_{2\alpha}$ related sweating was associated with release of epinephrine from the adrenal medulla and the decrease in rectal temperature in the $PGF_{2\alpha}$ treated mares was caused by sweating in the absence of shivering.

Trial 2. In the first trial, treatment of mares with $PGF_{2\alpha}$ - free acid and $PGF_{2\alpha}$ - tham salt on day 6 and 7 after foal heat decreased ($P < .01$) the time interval from foaling to the second estrus by approximately 10 days. Fertility was not affected by $PGF_{2\alpha}$ since eight of nine treated (80%) and five of five control mares conceived on the second estrus after foaling. Results suggested that the use of $PGF_{2\alpha}$ after foal heat provides a feasible approach to shortening the interval from foaling to rebreeding thus allowing the uterus a longer period of time to involute and possibly circumventing some of the problems associated with breeding at foal heat. Since a relatively small number of mares were available for the 1974 trial, the experiment was repeated in 1975 using the commercial form of $PGF_{2\alpha}$ - tham salt, Prostin $F_{2\alpha}$®.

In trial 2, a total of 16 Quarter Horse mares ranging from 3 to 20 yr. of age were assigned to two treatment groups. Nine mares were assigned to the $PGF_{2\alpha}$ treatment and seven served as controls. On day 6 and day 7 after foal estrus, treatment mares were given 15 mg. intramuscular (IM) injections of Prostin $F_{2\alpha}$® ($PGF_{2\alpha}$). Control mares were injected with 3 ml (IM) of sterile saline.

Estrus and ovulation data for $PGF_{2\alpha}$ treated and control mares are presented in table 14. The mean interval from foaling to the onset of foal estrus was similar for treated ($9.4 \pm .8$ days) and control ($10.1 \pm .9$ days) mares and is in agreement with the values observed in the initial trial and with those reported in the literature (Day, 1939 and Nishikawa and Hafez, 1968). Treated mares returned to estrus $5.1 \pm .6$ days and control mares $12.3 \pm .7$ days ($P < .01$) after the initial injection of $PGF_{2\alpha}$ and sterile saline. In the initial study treated mares showed estrus 5.0 days and control mares 17.0 days after the first injection of $PGF_{2\alpha}$ or saline. These data compare favorably with those of Tolksdorff (1975) and Witherspoon et al. (1975) in studies on the lactating postpartum mare.

The mean time interval between the first Prostin $F_{2\alpha}$® injection and ovulation was shorter ($P < .01$) in the treated females ($8.8 \pm .7$ days) than in the saline injected controls ($17.2 \pm .8$ days). These intervals from injection to ovulation confirm results from trial 1 and are in agreement with data reported by Douglas and Ginther (1975a).

TABLE 14. ESTRUS AND OVULATION IN PROSTAGLANDIN $F_{2\alpha}$ TREATED AND CONTROL MARES (TRIAL 2).

Interval between:	Treated (days) Prostin $F_{2\alpha}$® ($PGF_{2\alpha}$)[a]	Control (days) Saline[b]
Parturition and foal heat	9.4 ± .8[c]	10.1 ± .9
First injection and estrus	5.1 ± .6**	12.3 ± .7
First injection and ovulation	8.8 ± .7**	17.2 ± .8
Onset of 2nd estrus and ovulation	3.7 ± .5	5.0 ± .5
Ovulation and end of 2nd estrus	.8 ± .2	.4 ± .2
Foal heat and 2nd estrus	11.2 ± .6**	18.2 ± .7
Foaling and 2nd estrus	23.5 ± 1.0**	32.3 ± 1.1
Foaling and 2nd estrus ovulation	27.2 ± 1.1**	37.3 ± 1.3

[a] Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat (9 mares).

[b] Administered 3ml of sterile saline on days 6 and 7 after end of foal heat (7 mares).

[c] Least square mean ± standard error.

** Significantly shorter ($P < .01$) than controls.

All treated and control mares ovulated during the second estrus postpartum with intervals between the onset of estrus and ovulation of 3.7 $\pm$ .5 and 5.0 $\pm$ .5 days, respectively, thus confirming results from the initial trial. Consequently the finding of Noden et al. (1974) that the interval from onset of estrus to ovulation was longer in $PGF_{2\alpha}$ treated cycling mares can not be extended to include lactating postpartum mares.

Treatment of mares with $PGF_{2\alpha}$ had no effect on the interval from ovulation to the end of estrus since treated mares ovulated .8 $\pm$ .2 days and control mares .4 $\pm$ .2 days prior to the end of the second estrus period. Although these intervals are slightly shorter than values noted in trial 1, they are within the range for normal cycling mares as reported by Day (1939) and Nishikawa and Hafez (1968).

The average interval between the end of foal estrus and onset of the next estrus (interestrual period) was shorter ($P < .01$) for $PGF_{2\alpha}$ treated mares (11.2 $\pm$ .6 days) than for controls (18.2 $\pm$ .7 days). This interestrual interval was nearly identical to that observed for treated mares in the initial trial and agrees with data reported in the literature (Noden et al., 1974) for normal cycling mares following the use of $PGF_{2\alpha}$.

Treatment of mares with $PGF_{2\alpha}$ also shortened ($P < .01$) the interval between foaling and the second postpartum estrus by 8.8 days (figure 16). Furthermore there was a

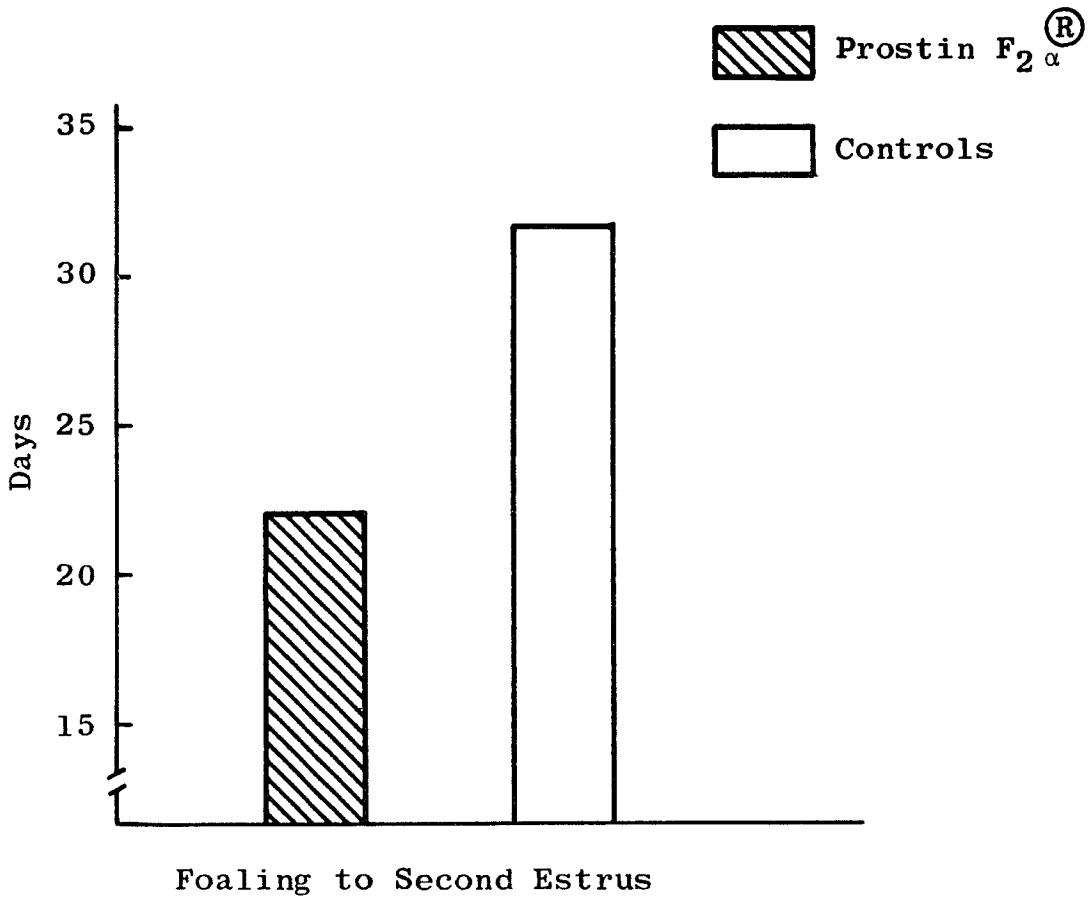

Figure 16. The time interval between foaling and the second postpartum estrus in treated and control mares (trial 2).

corresponding 10.1 day decrease ($P < .01$) in the interval from foaling to the second estrus ovulation. The ultimate result was a shortening of the time from foaling to rebreeding similar to that reported for trial 1.

A summary of the data on duration of estrus and reproductive efficiency is given in table 15. Duration of foal estrus and length of the second estrus postpartum were not significantly different between treated and control mares. Treated mares exhibited foal estrus for a mean of $3.4 \pm .5$ days compared with $4.6 \pm .6$ days for control mares. Duration of the second behavorial estrus was $4.4 \pm .4$ days in $PGF_{2\alpha}$ treated females and $5.4 \pm .5$ days for controls. Thus treatment of postpartum lactating mares with $PGF_{2\alpha}$ does not appear to affect duration of the posttreatment estrus.

In contrast to results of the initial trial, the conception rate in trial 2 was somewhat lower for $PGF_{2\alpha}$ treated mares (44%) than for saline injected controls (85%). However the number of stallion services per conception was similar for treated ($1.7 \pm .2$) and control ($1.6 \pm .3$) mares. The lowered fertility in treated mares can be accounted for, at least in part, by the fact that these females were mated to a stallion of questionable fertility. Although initial semen evaluation revealed no indication of a fertility problem, subsequent breeding to this stallion resulted in a 50% conception rate at first service compared to 91% for mares bred to the other stallion used in this

TABLE 15. DURATION OF ESTRUS AND REPRODUCTIVE EFFICIENCY OF PROSTAGLANDIN $F_{2\alpha}$ TREATED AND CONTROL MARES (TRIAL 2).

Item	Treated	Control
	Prostin $F_{2\alpha}$® ($PGF_{2\alpha}$)[a]	Saline[b]
Duration of foal estrus, days	3.4 ± .5[c]	4.6 ± .6
Duration of 2nd estrus, days	4.4 ± .4	5.4 ± .5
Conception rate, %	44	85
Services per conception, no.	1.7 ± .2	1.6 ± .3

[a] Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat (9 mares).

[b] Administered 3ml of sterile saline on days 6 and 7 after end of foal heat (7 mares).

[c] Least square mean ± standard error.

study. Since conception rate was not affected by $PGF_{2\alpha}$ treatment during the initial trial, it seems reasonable to assume that $PGF_{2\alpha}$ was not responsible for the lowered fertility in treated mares in the present trial.

The luteolytic effect of $PGF_{2\alpha}$ was confirmed by measuring progestin levels in blood samples collected from mares 15 minutes prior to and following each Prostin $F_{2\alpha}$® ($PGF_{2\alpha}$) injection and daily thereafter until the onset of estrus. Changes in plasma progestin levels in response to $PGF_{2\alpha}$ or saline injections are presented graphically in figure 17. Mean plasma progestin levels increased from $3.3 \pm .7$ ng/ml 15 min. before to 4.1 ± 1.0 ng/ml 15 min. after the first injection of $PGF_{2\alpha}$. Blood progestin concentrations then dropped rapidly to $1.2 \pm .4$ ng/ml 15 min. prior to the second injection of $PGF_{2\alpha}$ and remained at relatively low levels until the onset of estrus which occurred on the average $5.1 \pm .6$ days following the first $PGF_{2\alpha}$ injection. Pretreatment blood progestin levels were not significantly different between treated and control mares. However progestin levels in the $PGF_{2\alpha}$ treated mares were lower ($P < .01$) than the saline treated controls on days 7, 8, 9, 11 and 12 after foal heat (table 16). Blood progestin levels in the control females remained between 4.9 ± 1.3 and $7.1 \pm .4$ ng/ml during the posttreatment period. The decline in plasma progestin levels following $PGF_{2\alpha}$ treatment in the present trial is similar to that observed for treated females in trial 1 and is in agreement with

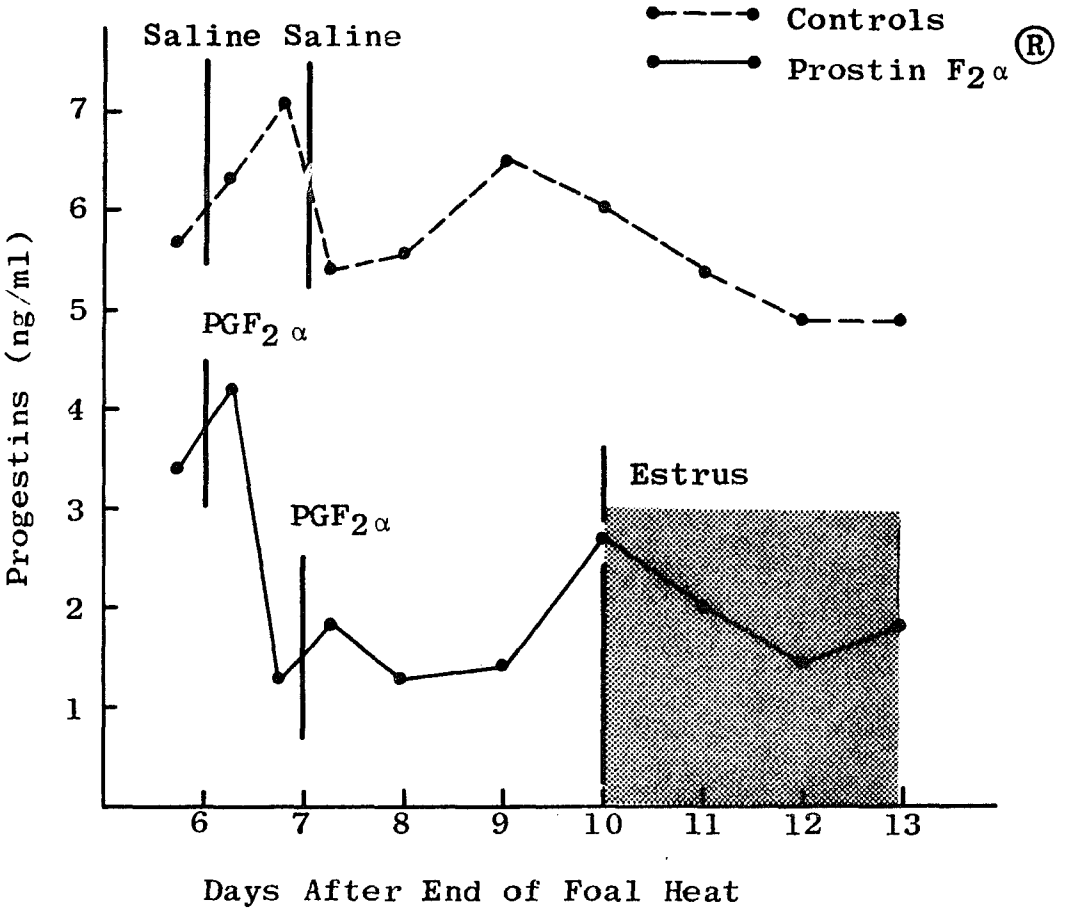

Figure 17. Mean progestin levels in the peripheral plasma of treated and control mares (trial 2).

TABLE 16. PLASMA PROGESTIN LEVELS IN PROSTAGLANDIN $F_{2\alpha}$ TREATED AND CONTROL MARES (TRIAL 2).

Days after foal heat[a]	Progestins (ng/ml)		Progestins (ng/ml)	
	n[b]	Prostin $F_{2\alpha}$®[c]	n[d]	Saline[e]
6 15 min. before inject.	8	3.3 ± .7[f]	6	5.6 ± .8
15 min. after inject.	9	4.1 ± 1.0	7	6.4 ± 1.2
7 15 min. before inject.	9	1.2 ± .4**	7	7.1 ± .4
15 min. after inject.	9	1.8 ± .5**	7	5.4 ± .6
8	9	1.2 ± .8**	7	5.6 ± .9
9	8	1.3 ± .6**	6	6.5 ± .7
10	5	2.7 ± 1.4	7	6.0 ± 1.2
11	7	2.0 ± .7**	6	5.4 ± .7
12	5	1.4 ± .5**	4	4.9 ± .5
13	2	1.9 ± 1.8	4	4.9 ± 1.3

[a]Blood samples collected 15 min. prior to and following each Prostin F_2 ® or sterile saline injection and daily there after until induction of estrus.

[b]Number of samples contributing mean values for progestins.

[c]Administered 15 mg (IM) injection of Prostin F_2 R on days 6 and 7 after end of foal heat.

[d]Number of samples contributing mean values for progestins.

[e]Administered 3 ml injection of sterile saline on days 6 and 7 after end of foal heat.

[f]Mean ± standard error.

** Significantly lower ($P < .01$) than controls.

trends reported by Tolksdorff (1975) and Witherspoon et al. (1975) in lactating postpartum mares following RS 9390 treatment. The precipitous decline in plasma progestin levels following treatment with $PGF_{2\alpha}$ indicates that this compound has a luteolytic effect in the postpartum lactating mare comparable to that reported for the cycling dry mare.

Mares in trial 2 were again observed for side effects following each Prostin $F_{2\alpha}$® injection and a sweating response was noted identical to that described in trial 1. The sweating started 15 to 20 min. after the $PGF_{2\alpha}$ injections and persisted for approximately 2 hours. On the basis of results from the present study (trial 1 and trial 2) and those of Lauderdale et al. (1975b) it is apparent that the side effects of luteolytic doses of $PGF_{2\alpha}$ in mares are transitory. Furthermore it appears that the administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$ - free acid, $PGF_{2\alpha}$ - tham salt and Prostin $F_{2\alpha}$®) on days 6 and 7 after the end of foal heat significantly reduces the interval from foaling to rebreeding compared to control mares. Fertility does not appear to be affected by $PGF_{2\alpha}$ since conception rates in the two trials were not significantly different between treated and control mares.

General Discussion

Numerous investigators have reported that reproductive performance in horses is low when compared to other domestic animals. Contributing to the poor reproductive efficiency is a relatively high abortion rate in mares and a failure to properly synchronize mating with ovulation. A comparison of steroid levels in "normal" foaling mares with those that habitually abort may lead to a greater understanding of the causes of equine abortion.

In normal foaling mares Holtan et al. (1975) reported that progesterone concentrations followed a trend similar to that found in the cow (Pope et al., 1969; Donaldson et al., 1970; Stabenfeldt et al., 1970; Henricks et al., 1972; Smith et al., 1973) and sow (Tillson and Erb, 1967; Killian et al., 1973; Molokwu and Wagner, 1973; Edqvist et al., 1974; Robertson and King, 1974; Ash and Heap, 1975) with levels decreasing rapidly during the 5 days before parturition and reaching basal levels 1 to 3 days postpartum. Similarly in the present study, progestin levels in the mare remained relatively stable from day 7 through day 3 prepartum. Levels then dropped precipitiously during the 48 hr. preceeding parturition and reached nondetectable levels by day 1 postpartum. The progestin drop to nondetectable levels in the dam after foaling lends support to the concept of placental production of progesterone during late gestation in the mare (Short, 1959). In contrast Allen

and Hadley (1974) observed no fall in progesterone values before conceptual loss occurred on day 23 and 28 of gestation in two mares. However, these pregnancies were accompanied by lower than average blood progesterone concentrations indicating that low production of this hormone may have been responsible for the early fetal deaths.

According to Nishikawa (1959), abortion in the mare occurs most frequently 150 days following breeding. Nishikawa (1959) further noted that administration of the synthetic estrogen, diethylstilbestrol increased the life span of the accessory corpora lutea and increased urinary pregnanediol excretion while decreasing abortion rates. In mares completing gestation Nett et al. (1973) observed that E_1 (estrone, equilin and equilenin) levels decline during the month before foaling with a precipitious drop occurring at parturition, whereas, E_2 (estradiol) levels remain relatively constant during this time period. In a mare that aborted at 203 days postinsemination, Nett et al. (1973) found that the concentrations of E_1 and E_2 prior to abortion followed a pattern similar to that observed in mares which completed gestation, suggesting that a lack of estrogens was not the cause of conceptual loss in this mare. In the present study of normal foaling mares, total estrogen levels remained essentially unchanged from day 7 through day 3 prepartum. Levels then declined rather consistently until day 1 or 2 postpartum. In contrast, estrogen levels in the cow (Mellin and Erb, 1965;

Erb et al., 1968; Hunter et al., 1970; Henricks et al., 1972; Hoffmann et al., 1973; Smith et al., 1973), sow (Molokwu and Wagner, 1973; Edqvist et al., 1974; Robertson and King, 1974; Ash and Heap, 1975) and ewe (Challis 1971; Robertson and Smeaton, 1973) appear to increase near term and reach a peak on or near the day of parturition.

The significance of the concurrent decline in total progestins and estrogens near the time of parturition in the present study is uncertain but was consistent in all mares and with the literature (Nett et al., 1973; Holtan et al., 1975) suggesting that it may be involved in the initiation of parturition in the equine. However these findings are in disagreement with the theory in cows that a rise in plasma estrogen in the presence of a declining progesterone level is required for parturition and is inconsistent with the idea that in the bovine (Henricks et al., 1972) an increasing estrogen level is the governing factor in the initiation of parturition.

To our knowledge the role of corticoids in equine parturition has not been studied. However Alm et al. (1974) did report that the administration of massive doses of the synthetic corticoid, dexamethasone during late pregnancy (days 321 through 324 of gestation) causes premature parturition in mares. Corticoid levels in the present study were variable, increasing from day 3 prepartum to the day of foaling in trial 1 and decreasing on the day

of parturition in trial 2. Since blood samples for hormone determination were collected less frequently in trial 2 compared to trial 1, peaks in corticoid concentrations at the time of foaling in trial 2 may have been missed. From the results of this study the role of corticoids at parturition in the mare is unclear, however the time of peak concentration in the initial trial suggests that the rise in corticoids at the time of foaling is a result of the stress of foaling rather than an initiator of parturition.

Studies in the cow (Wagner, 1970; MacAdam and Eberhart, 1972; Wagner and Oxenreider, 1972) and sow (Killian et al., 1973) have demonstrated that morning blood samples are significantly higher in corticoid concentration than evening collected samples. In the present study corticoid levels in the mare were also higher in the morning compared to the evening samples indicating that the time of blood sample collection must be taken into consideration when monitoring corticoid concentrations in the periparturient mare.

In another phase of the study, hormone levels in the newborn foals were monitored to determine their possible involvement in the initiation of parturition. Early research by Short (1959) involving only 3 foals indicated that progesterone concentrations were higher in umbilical cord blood when compared to mares at parturition. In data reported herein, plasma progestin levels were also greater in foals than in the peripheral blood of the mare on the

day of parturition suggesting the possibility of a fetal source of progestins during late pregnancy. Foal progestin levels subsequently declined during the first 24 hr. postpartum.

Plasma estrogen levels in the newborn foals were similar to maternal values at foaling and remained rather constant during the postpartum study period (24 to 48 hrs. after foaling). This observation, together with the findings of Raeside et al. (1973) that fetal gonadectomy leads to a fall in estrogen excretion by the mare, suggests that the feto-placental unit during late pregnancy contributes to the estrogen pool in the mare.

Postnatal corticoid values were highest immediately after birth and subsequently declined at 24 and 48 hr. postpartum. In ruminants a gradual rise in fetal plasma cortisol begins during the last few days of gestation,but further increases may occur at or just after parturition (Bassett and Thorburn, 1969; Nathanielsz et al., 1972; Comline et al., 1974). Cortisol production rate in the lamb fetus increases from .4 ug/kg/min. to 10 mg/kg/day just before parturition and has been implicated as one of the major mechanisms leading to the initiation of parturition in sheep (Liggins et al., 1973). Whether there is a comparable prenatal corticoid surge in the fetal foal just before birth is still unknown.

Another factor contributing to the poor reproductive efficiency of the equine is the practice of breeding mares at the first postpartum estrus. Previous studies have indicated that mating of mares at foal estrus carries a greater risk of conception failure and early pregnancy loss than mating at subsequent estrus periods (Williams, 1942; Jennings, 1950; Trum, 1950). The greater risk of conception failure has been attributed to reduced effectiveness of uterine defense mechanisms and incomplete repair of the uterine epithelium by the usual time of foal heat. Andrews and McKenzie (1941) reported that the uterine epithelium does not return to normal until 13 to 25 days postpartum. Assuming these observations to be correct, it seemed feasible to pass mares at foal heat and administer the luteolytic agent, $PGF_{2\alpha}$, during the subsequent luteal phase to induce estrus and thus allow more time for uterine involution and endometrial repair. The most significant result of this approach was that the time interval from foaling to second estrus ovulation was decreased ($P < .01$) in the $PGF_{2\alpha}$ treated females resulting in a decrease in the time interval from foaling to rebreeding while allowing more time for uterine involution. Although not studied in the present experiment, Loy et al. (1975) observed that at day 15 the uterine mucosa of the postpartum mare had a more regular appearance than at day 5 and 10 postpartum with a more abundant glandular and luminal epithelium and fewer inflammatory cells.

In contrast to the findings of Noden et al. (1974) who observed that the duration of estrus and the interval from onset of estrus to ovulation were longer after $PGF_{2\alpha}$ treatment than during control estrus, the present experiment failed to demonstrate any significant effect of $PGF_{2\alpha}$ on length of posttreatment estrus or on the length of the interval from onset of estrus to ovulation in the foaling mare. The estrus which began after $PGF_{2\alpha}$ treatment was similar in every measured criterion to control estrus periods indicating that $PGF_{2\alpha}$ is not detrimental to estrus or ovulation.

According to Berwyn-Jones and Irvine (1974) the induction of a fertile estrus requires gonadotropin stimulation and a low progesterone profile. While prostaglandins effectively promote behavioural estrus by progestin withdrawal as demonstrated in the present experiment and in the literature (Allen and Rossdale, 1973; Allen and Rowson, 1973; Allen et al., 1974; Noden et al., 1974; Thompson and Witherspoon, 1974; Douglas and Ginther, 1975a,b; Tolksdorff, 1975; Witherspoon et al., 1975) there is no evidence that moderately elevated plasma prostaglandin levels promote gonadotropin release directly. The sharp fall in plasma progestin levels following $PGF_{2\alpha}$ treatment observed in this study, taken in conjunction with the observation that all mares exhibited estrus within 5 days of treatment with the compound, indicates that $PGF_{2\alpha}$ is an effective luteolysin in the postpartum lactating mare.

Tolksdorff (1975) and Witherspoon et al. (1975) presented data to suggest that fertility in the lactating postpartum mare was not adversely affected by treatment with the $PGF_{2\alpha}$ analogue RS 9390. Similarly in trial 1 of the present study conception rates at the second postpartum estrus were high in both treated and control mares indicating that $PGF_{2\alpha}$ treatment is not detrimental to fertility. Since conception rate at the induced estrus was considerably higher than values reported for mares bred at foal heat (Williams, 1942; Jennings, 1950; Trum, 1950) it may be postulated that the uterine epithelium had returned to normal at this time. However, in trial 2, fertility was somewhat depressed in the $PGF_{2\alpha}$ treated mares when compared to controls. This lowered fertility in the treated mares in trial 2 can be accounted for, at least in part, by the fact that these mares were mated to a stallion of questionable fertility. Although initial semen evaluation revealed no indication of a fertility problem, subsequent breeding to this stallion resulted in a marked reduction in conception rate at first service compared to mares bred to the other stallion used in the study. Further examination of this stallion revealed that ejaculation was frequently accompanied by urination before withdrawl. In view of this finding and since $PGF_{2\alpha}$ treatment had no effect on conception rate in the first trial, it seems reasonable to assume that

$PGF_{2\alpha}$ was not responsible for the lowered fertility in treated mares in trial 2. However, this assumption awaits further investigation.

The results of this study suggest that by injecting $PGF_{2\alpha}$ on day 6 and day 7 after foal heat a high percentage of mares may be mated successfully within a month of foaling. Further studies are warranted to compare the efficiency of breeding mares at the foal heat or waiting for the next estrus with attendant risks of lactation diestrus or a system of breeding based on the use of $PGF_{2\alpha}$ after the foal heat.

CHAPTER V

SUMMARY

Two studies were conducted during the breeding seasons of 1974 and 1975 to monitor steroid levels in the peripartum mare and newborn foal (Experiment I) and to determine the feasibility of using prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) to control the estrous cycle of the postpartum lactating mare (Experiment II). In trial 1 of the first study, plasma progestin, estrogen and corticoid levels were determined in nine Quarter Horse mares during the 7 days prior to parturition through 2 days postpartum. Blood samples were collected at 6 hr. intervals by jugular puncture. Progestin and corticoid concentrations were determined by competitive protein binding and estrogen levels by radioimmunoassay. Steroid levels were also determined on a plasma sample from each of nine foals at birth and on six foals 24 hr. postpartum. Plasma progestin concentrations in the mares decreased ($P < .01$) from 13.4 $\pm$ .6 ng/ml on day 3 prepartum to 3.2 $\pm$ .5 ng/ml on the day of parturition. Estrogen levels also declined ($P < .01$) from day 3 prior to foaling (306.2 $\pm$ 11.4 pg/ml) to the day of parturition (193.4 $\pm$ 9.0 pg/ml). However corticoid concentrations increased ($P < .01$) from 85.8 $\pm$ 10.8 ng/ml on day 3 before parturition to a peak of 140.0 $\pm$ 9.8 ng/ml on the day of foaling. A considerable amount of individual variation in steroid levels existed among mares. There was no significant diurnal variation of progestin, estrogen or

corticoid levels in the pre- or postpartum mares, but corticoid levels tended to be higher in morning than in evening samples.

Mean plasma progestin concentrations in the newborn foals decreased ($P < .05$) from 16.4 ± 1.9 ng/ml at birth to 5.6 ± 2.6 ng/ml 24 hr. postpartum, but estrogen levels were similar at foaling (171.4 ± 5.9 pg/ml) and 24 hr. later (167.9 ± 5.0 pg/ml). Foal corticoid levels dropped ($P < .05$) from 114.3 ± 8.7 ng/ml at parturition to 69.4 ± 12.2 ng/ml 24 hr. postpartum. Sex had no effect on progestin or estrogen levels in the newborn foals, however estrogen levels were higher ($P < .05$) in the newborn fillies (183.2 ± 4.5 pg/ml) than in the newborn colts (156.0 ± 6.4 pg/ml).

The study was repeated in 1975 using a total of nine mares. Trial 2 was similar to the previous trial except that blood samples for hormone determination were collected at 12 hr. intervals. The trend in plasma progestin levels in trial 2 was in close agreement with that observed in the initial trial except that values were considerably lower. Progestin levels dropped ($P < .01$) precipitiously from 5.3 ± .6 ng/ml on day 3 prepartum to nondetectable levels on the day of parturition and remained at near non-detectable levels through day 2 postpartum. Plasma estrogens followed a pattern similar to that described in the 1974 trial with levels declining ($P < .01$) from 360.9 ± 14.2 ng/ml on day 3 prior to foaling and continuing

through the day of foaling (198.8 ± 12.7 pg/ml). Mean corticoid concentrations in trial 2 were lower than those in the first trial with levels varying between 78.4 ± 8.6 ng/ml and 93.5 ± 8.2 ng/ml until the day before parturition. In contrast to the peak in corticoid levels observed on the day of parturition in the first trial, levels in trial 2 decreased on the day of foaling (77.9 ± 7.4 ng/ml). Again there was considerable ($P < .01$) individual variation in steroid levels among mares. Plasma progestin and estrogen levels showed no diurnal variation, however, mean corticoid levels were higher ($P < .01$) in morning (90.7 ± 3.4 ng/ml) than in evening (66.2 ± 3.9 ng/ml) collected samples.

Progestin concentrations in the newborn foals decreased ($P < .01$) from 2.6 ± .5 ng/ml at birth to .8 ± .6 ng/ml 24 hr. later and further declined to .3 ± .5 ng/ml at 48 hr. postpartum. However plasma estrogen levels in the neonate foals remained relatively unchanged during this time and were 188.9 ± 17.4 pg/ml on the day of parturition, 173.4 ± 16.6 pg/ml on day 1 and 177.2 ± 17.4 pg/ml on day 2 after foaling. Circulating corticoid levels in the newborn foals decreased from 59.7 ± 16.6 ng/ml at foaling to 35.8 ± 18.4 ng/ml 24 hr. later and continued to decrease to 7.4 ± 17.0 ng/ml at 48 hr. postpartum. There was no significant difference in steriod levels between colts and fillies.

In the second study two trials were conducted to determine if prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) could be used to induce estrus in mares shortly after foal heat and thereby

reduce the time from foaling to rebreeding while circumventing the undesirable effects of breeding on the first postpartum estrus. In the initial trial, 14 Quarter Horse mares were allotted to three treatment groups. On day 6 and day 7 after the end of foal estrus, four mares were given a 10 mg subcutaneous injection (SC) of $PGF_{2\alpha}$ - free acid and five mares were injected with 15 mg (SC) of $PGF_{2\alpha}$ - tham salt. Control mares were given injections of an equal volume of sterile saline. The mean interval from foaling to the onset of foal estrus was similar for the $PGF_{2\alpha}$ - free acid (8.5 $\pm$ 1.3 days), $PGF_{2\alpha}$ - tham salt (10.4 $\pm$ 1.1 days) and control (7.2 $\pm$ 1.1 days) females. Mares treated with $PGF_{2\alpha}$ - free acid and $PGF_{2\alpha}$ - tham salt exhibited behavorial estrus 5.0 $\pm$ 2.7 and 5.0 $\pm$ 2.5 days following the initial injection compared to 17.0 $\pm$ 2.5 days for controls ($P < .01$). All treated and control mares ovulated on the second estrus postpartum with mean time intervals from injection to ovulation of 9.0 $\pm$ 3.2 and 10.2 $\pm$ 2.8 days for the $PGF_{2\alpha}$ - free acid and $PGF_{2\alpha}$ - tham salt treated females ($P < .01$) compared to 21.8 $\pm$ 2.8 days for the saline injected controls. The interval from foal heat to the onset of the second estrus (interestrual period) was shorter ($P < .01$) in the $PGF_{2\alpha}$ - free acid (11.0 $\pm$ 2.7 days) and $PGF_{2\alpha}$ - tham salt (11.4 $\pm$ 2.5 days) treated mares than in the controls (24.8 $\pm$ 2.5 days). In addition the interval between foaling and the onset of the second estrus was decreased

($P < .01$) as a result of treatment with $PGF_{2\alpha}$ - free acid (23.0 $\pm$ 2.3 days) or $PGF_{2\alpha}$ - tham salt (24.6 $\pm$ 2.1 days) as compared to saline injected control mares (34.2 $\pm$ 2.1 days). Also, the time between foaling and second estrus ovulation was decreased ($P < .01$) in the treated mares (27.0 $\pm$ 2.7 days for $PGF_{2\alpha}$- free acid and 29.2 $\pm$ 2.4 days for $PGF_{2\alpha}$- tham salt) as compared to the controls (39.0 $\pm$ 2.4 days). Thus the time interval from foaling to rebreeding was reduced in the treated mares. The form of $PGF_{2\alpha}$ (free acid or tham salt) used, however, did not seem to matter since intervals from foaling to estrus and ovulation were similar for both treated groups.

The estrus following $PGF_{2\alpha}$ treatment resembled control estrus in every measured criterion. Ovulation occurred 4.0 $\pm$ 1.0, 5.2 $\pm$ .9 and 4.8 $\pm$ .9 days after the onset of estrus in $PGF_{2\alpha}$ - free acid, $PGF_{2\alpha}$ - tham salt and control mares, respectively. Neither $PGF_{2\alpha}$ - free acid nor $PGF_{2\alpha}$ - tham salt altered the interval from ovulation to the end of estrus since treated mares ovulated 1.0 $\pm$ .2 and 1.2 $\pm$ .2 days and controls 1.0 $\pm$ .2 days before the end of estrus. Also duration of the second estrus was similar for $PGF_{2\alpha}$ - free acid (5.0 $\pm$ 1.0 days), $PGF_{2\alpha}$- tham salt (6.4 $\pm$ .9 days) and control (5.8 $\pm$ .9 days) mares.

Treatment of mares with $PGF_{2\alpha}$ did not appear to adversely affect fertility since all of the $PGF_{2\alpha}$ - free acid and control mares and four of five $PGF_{2\alpha}$ - tham salt

treated females conceived on the second estrus after foaling. Breeding efficiency was similar for all treatments with 2.2 ± .6, 2.2 ± .5 and 2.4 ± .5 stallion services per conception for the $PGF_{2\alpha}$ - free acid, $PGF_{2\alpha}$ - tham salt and control groups, respectively.

Treatment with $PGF_{2\alpha}$ - tham salt resulted in a rapid drop in progestin levels from a mean pretreatment level of 2.9 ± 1.7 ng/ml to .4 ± .2 ng/ml 15 min. following the second injection. Levels remained at less than 1.5 ng/ml until the onset of estrus which occurred on the average 5 days after the first $PGF_{2\alpha}$ injection. Profuse sweating occurred in mares 15 to 20 min. after treatment with $PGF_{2\alpha}$ - free acid or $PGF_{2\alpha}$ - tham salt and ceased 2 hr. following treatment. No other side effects were observed.

The experiment was repeated in 1975 using the commerical form of $PGF_{2\alpha}$ - tham salt, Prostin $F_{2\alpha}$®. On day 6 and 7 after foal estrus nine treatment mares were given 15 mg intramuscular (IM) injections of Prostin $F_{2\alpha}$® and seven control mares were injected with 3 ml (IM) of sterile saline. The mean time interval between foaling and onset of foal estrus was similar for treated (9.4 ± .8 days) and control (10.1 ± .9 days) mares. Treated mares returned to estrus 5.1 ± .6 days and control mares 12.3 ± .7 days ($P < .01$) after the initial injection of Prostin $F_{2\alpha}$® or sterile saline. Also, the interval between the first Prostin $F_{2\alpha}$® injection and ovulation was shorter ($P < .01$)

for the treated females (8.8 ± .7 days) than for the saline injected controls (17.2 ± .8 days). Futhermore, the interestrual interval was shorter ($P < .01$) for treated mares (11.2 ± .6 days) than for controls (18.2 ± .7 days). Treatment of mares with Prostin $F_{2\alpha}$® shortened ($P < .01$) the interval between foaling and the second postpartum estrus by 8.8 days resulting in a 10.1 day decrease ($P < .01$) in the interval from foaling to second estrus ovulation. The ultimate result was a shortening of the time from foaling to rebreeding similar to that reported for trial 1.

The conclusion that $PGF_{2\alpha}$ does not adversely affect estrus in the postpartum lactating mare was confirmed by results of trial 2. All treated and control mares ovulated during the second estrus postpartum with intervals between the onset of estrus and ovulation of 3.7 ± .5 and 5.0 ± .5 days, respectively. Also, Prostin $F_{2\alpha}$® had no effect on the interval from ovulation to end of estrus since treated mares ovulated .8 ± .2 days and control mares .4 ± .2 days prior to the end of the second estrus. Furthermore, the length of the second estrus after foaling was not significantly different between treated (4.4 ± .4 days) and control (5.4 ± .5 days) mares.

In contrast to the results of the initial trial the conception rate in trial 2 was somewhat lower for treated mares (44%) than for saline injected controls (85%). However, the number of stallion services per

conception was similar for treated (1.7 ± .2) and control (1.6 ± .3) mares.

The luteolytic effect of Prostin $F_{2\alpha}$® was confirmed by measuring progestin levels in treated and control mares. Blood progestin concentrations dropped rapidly from a mean pretreatment level of 3.3 ± .7 ng/ml to 1.2 ± .4 ng/ml on the second day of treatment and remained at relatively low levels until the onset of estrus. Progestin levels were lower ($P < .01$) in Prostin $F_{2\alpha}$® treated mares than in the saline injected controls on days 7, 8, 9, 11 and 12 after foal heat. Mares in trial 2 were also observed for side effects following each Prostin $F_{2\alpha}$® injection and a transitory sweating response was noted identical to that described in trial 1.

The results of the foregoing studies indicate that circulating progestin and estrogen levels decline during the 48 hr. preceeding parturition and that corticoid concentrations are quite variable in the periparturient mare. Also these data suggest that progestin and corticoid levels decline in the Quarter Horse foal during the first 24 to 48 hr. postpartum. Futhermore, it appears that the administration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$ - free acid, $PGF_{2\alpha}$ - tham salt and Prostin $F_{2\alpha}$®) on days 6 and 7 after the end of foal estrus significantly reduces the interval from foaling to rebreeding compared to control mares. Fertility does not appear to be affected by $PGF_{2\alpha}$ since

conception rates in the two trials were not significantly different between treated and control mares. The decrease in progestin levels following treatment with $PGF_{2\alpha}$ confirms that the drug has a luteolytic effect on the postpartum lactating mare.

CHAPTER VI

CONCLUSIONS

The results of the present study warrant the following conclusions:

1. Peripheral plasma progestin and estrogen levels in the mare decline during the final 48 hr. preceeding parturition, while corticoid concentrations are quite variable at this time.
2. A diurnal variation in circulating progestin and estrogen levels does not occur in the periparturient mare; however, corticoid levels tend to be higher in morning than in evening collected blood samples.
3. Plasma progestin and corticoid levels decline in Quarter Horse foals during the first 24 hr. postpartum while estrogen levels remain fairly constant during this time.
4. Sex has no effect on progestin or corticoid concentrations in newborn foals,but estrogen levels may be higher in newborn fillies than in colts.
5. Treatment with $PGF_{2\alpha}$ - free acid, $PGF_{2\alpha}$ - tham salt or Prostin $F_{2\alpha}$ ® on day 6 and day 7 after foal heat results in a significant ($P< .01$) reduction in the intervals from (a) injection to onset of estrus, (b) injection to ovulation, (c) end of foal heat to onset of second estrus, and (d) end of foal heat to ovulation.

6. The interval from foaling to rebreeding on the second estrus postpartum is decreased in $PGF_{2\alpha}$ treated mares.
7. $PGF_{2\alpha}$ treatment has no effect on duration of estrus or ovulation.
8. Treatment of lactating postpartum mares with $PGF_{2\alpha}$ does not adversely affect fertility or breeding efficiency.
9. Treatment of mares with $PGF_{2\alpha}$ on day 6 and day 7 after foal heat causes luteolysis as demonstrated by a reduction in progestin levels following injection of the compound and a subsequent return to estrus within 5 days of treatment.

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APPENDIX

TABLE 1. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN PERIPARTURIENT MARES (TRIAL 1)

Source	df	Mean square
Mare	8	115.8**
Time	3	1.3
Day	9	331.0**
-7,-6,-5,-4,-3,-2,-1,0 vs 1,2	1	1507.8**
-7,-6,-5,-4, vs -3,-2,-1,0	1	74.7**
-7,-6, vs -5,-4	1	0.5
-3,-2, vs -1,0	1	1096.8**
-7 vs -6	1	14.6
-5 vs -4	1	8.7
-3 vs -2	1	15.8
-1 vs 0	1	593.3**
1 vs 2	1	0.3
Time x day	27	9.3
Error	160	8.1

** $P < .01$.

TABLE 2. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA ESTROGEN LEVELS IN PERIPARTURIENT MARES (TRIAL 1)

Source	df	Mean square
Mare	8	11432.2**
Time	3	2281.4
Day	9	58312.4**
-7,-6,-5,-4,-3,-2,-1,0 vs 1,2	1	362479.8**
-7,-6,-5,-4 vs -3,-2,-1,0	1	45708.4**
-7,-6 vs -5,-4	1	964.9
-3,-2 vs -1,0	1	77610.6**
-7 vs -6	1	3960.5
-5 vs -4	1	6430.3
-3 vs -2	1	13261.2**
-1 vs 0	1	57992.5**
1 vs 2	1	1379.4
Time x day	24	2655.5
Error	145	2038.8

** P <.01.

TABLE 3. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA CORTICOID LEVELS IN PERIPARTURIENT MARES (TRIAL 1)

Source	df	Mean square
Mare	8	25374.8**
Time	3	5107.8
Day	9	5357.0*
-7,-6,-5,-4,-3,-2,-1,0 vs 1,2	1	2100.6
-7,-6,-5,-4, vs -3,-2,-1,0	1	2635.5
-7,-6, vs -5,-4	1	1373.4
-3,-2 vs -1,0	1	25484.5**
-7, vs -6	1	2169.6
-5 vs -4	1	1620.8
-3 vs -2	1	2310.8
-1 vs 0	1	11850.6*
1 vs 2	1	19.1
Time x Day	26	1737.4
Error	151	2171.8

* $P < .05$.

** $P < .01$.

TABLE 4. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN NEWBORN FOALS (TRIAL 1)

Source	df	Mean square
Sex	1	0.87
Foal (sex)	7	58.62
Day	1	346.68*
Sex x day	1	11.40
Error (b)	4	31.95

* $P < .05$.

TABLE 5. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA ESTROGEN LEVELS IN NEWBORN FOALS (TRIAL 1)

Source	df	Mean square
Sex	1	990.08*
Foal (sex)	4	1987.93
Day	1	16.33
Sex x day	1	2296.33
Error (b)	1	81.00

* $P < .05$.

TABLE 6. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA CORTICOID LEVELS IN NEWBORN FOALS (TRIAL 1)

Source	df	Mean square
Sex	1	1797.56
Foal (sex)	7	5495.79
Day	1	6066.00*
Sex x day	1	501.81
Error (b)	4	678.80

* $P < .05$.

TABLE 7. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN PERIPARTURIENT MARES (TRIAL 2)

Source	df	Mean square
Mare	8	81.82**
Time	1	0.001
Day	9	77.05**
-7,-6,-5,-4,-3,-2,-1, 0 vs 1,2	1	372.4**
-7,-6,-5,-4, vs -3,-2,-1,0	1	54.1**
-7,-6 vs -5,-4	1	0.2
-3,-2 vs -1,0	1	181.1**
-7 vs -6	1	2.9
-5 vs -4	1	0.9
-3 vs -2	1	0.9
-1 vs 0	1	93.8**
1 vs 2	1	0.3
Time x day	9	1.91
Error	119	4.31

**P < .01.

TABLE 8. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA ESTROGEN LEVELS IN PERIPARTURIENT MARES (TRIAL 2)

Source	df	Mean square
Mare	8	12022.4**
Time	1	8719.3
Day	9	61291.8**
-7,-6,-5,-4,-3,-2,-1, 0 vs 1,2	1	289367.2**
-7,-6,-5,-4 vs -3,-2,-1,0	1	26642.1**
-7,-6 vs -5,-4	1	37.7
-3,-2 vs -1,0	1	121863.4**
-7 vs -6	1	78.7
-5 vs -4	1	11775.1*
-3 vs -2	1	6839.8
-1 vs -0	1	106875.4**
1 vs 2	1	2925.4
Time x day	9	1516.6
Error	120	2886.6

* P <.05.

** P <.01.

TABLE 9. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA CORTICOID LEVELS IN PERIPARTURIENT MARES (TRIAL 2)

Source	df	Mean square
Mare	8	7686.7**
Time	1	21141.5**
Day	9	2567.6**
-7,-6,-5,-4,-3,-2,-1, 0 vs 1,2	1	5851.2*
-7,-6,-5,-4, vs -3,-2,-1,0	1	1119.3
-7,-6 vs -5,-4	1	5042.2*
-3,-2 vs -1,0	1	37.6
-7 vs -6	1	6634.4**
-5 vs -4	1	32.4
-3 vs -2	1	887.5
-1 vs 0	1	1974.7
1 vs 2	1	1940.5
Time x day	9	1716.7
Error	117	999.8

* $P < .05$.

** $P < .01$.

TABLE 10. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN NEWBORN FOALS (TRIAL 2)

Source	df	Mean square
Sex	1	2.02
Foal (sex)	7	5.32
Day	2	10.80*
0 vs 1,2	1	20.68**
1 vs 2	1	.77
Sex x day	2	2.25
Error (b)	10	1.97

* P <.05.
** P <.01.

TABLE 11. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA ESTROGEN LEVELS IN NEWBORN FOALS (TRIAL 2)

Source	df	Mean square
Sex	1	1635.71
Foal (sex)	7	889.40
Day	2	463.45
0 vs 1,2	1	849.00
1 vs 2	1	54.10
Sex x day	2	541.65
Error (b)	11	2098.26

TABLE 12. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA CORTICOID LEVELS IN NEWBORN FOALS (TRIAL 2)

Source	df	Mean square
Sex	1	101.94
Foal (sex)	7	546.43
Day	2	4868.32
0 vs 1,2	1	7153.1
1 vs 2	1	2584.2
Sex x day	2	2286.42
Error (b)	10	2010.09

TABLE 13. LEAST SQUARES ANALYSIS OF VARIANCE FOR ESTRUS AND OVULATION IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES (TRIAL 1)

Source	df	Mean square: Parturition to foal heat	First injection to estrus	First injection to ovulation	Onset 2nd estrus to ovulation
Treatment	2	12.9	231.4**	238.2*	1.6
C vs F,T	1	16.1	466.0**	473.2**	0.13
F vs T	1	7.9	0.0	3.2	3.2
Error	11	6.6	31.1	41.2	4.3

TABLE 13. (Continued)

Source	df	Mean square: Ovulation to end of 2nd estrus	Foal heat to 2nd estrus	Foaling to 2nd estrus	Foaling to 2nd estrus ovulation
Treatment	2	0.06	296.5**	173.7**	192.1**
C vs F,T	1	0.03	592.7**	346.7**	380.2**
F vs T	1	0.09	0.4	5.7	10.7
Error	11	0.25	30.4	22.4	28.8

[a]Four mares administered 10 mg (SC) injection of $PGF_{2\alpha}$ - free acid (F) and five mares given 15 mg (SC) injection of $PGF_{2\alpha}$ - tham salt (T) on days 6 and 7 after end of foal heat.

[b]Five mares administered 1.5 ml sterile saline (C) on days 6 and 7 after end of foal heat.

* $P < .05$.

** $P < .01$.

TABLE 14. LEAST SQUARES ANALYSIS OF VARIANCE FOR DURATION OF ESTRUS AND REPRODUCTIVE EFFICIENCY IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES (TRIAL 1)

		Mean square			
Source	df	Duration of foal estrus	Duration of 2nd estrus	Conception rate	Services per conception
Treatment	2	1.5	2.2	0.06	0.05
C vs F, T	1	0.98	0.03	0.03	0.09
F vs T	1	1.8	4.37	0.08	0.08
Error	11	2.5	4.0	0.07	1.3

[a] Four mares administered 10 mg (SC) injection of $PGF_{2\alpha}$ - free acid (F) and five mares given 15 mg (SC) injection of $PGF_{2\alpha}$ - tham salt (T) on days 6 and 7 after end of foal heat.

[b] Five mares administered 1.5 ml sterile saline (C) on days 6 and 7 after end of foal heat.

TABLE 15. LEAST SQUARES ANALYSIS OF VARIANCE FOR ESTRUS AND OVULATION IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES (TRIAL 2)

		Mean square			
Source	df	Parturition to foal heat	First injection to estrus	First injection to ovulation	Onset 2nd estrus to ovulation
Treatment	1	1.9	202.6**	285.0**	7.0
Error	14	6.4	3.7	4.8	1.8

TABLE 15. (Continued)

Source	df	Mean square: Ovulation to end of 2nd estrus	Mean square: Foal heat to 2nd estrus	Mean square: Foaling to 2nd estrus	Mean square: Foaling to 2nd estrus ovulation
Treatment	1	0.48	196.4**	300.1**	398.7**
Error	14	0.37	3.8	8.4	11.6

[a] Nine mares administered 15 mg (IM) injection of Prostin $F_{2\alpha}$ ® on days 6 and 7 after end of foal heat.

[b] Seven mares administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

** P <.01.

TABLE 16. LEAST SQUARES ANALYSIS OF VARIANCE FOR DURATION OF ESTRUS AND REPRODUCTIVE EFFICIENCY IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES (TRIAL 2)

		Mean square			
Source	df	Duration of foal estrus	Duration of 2nd estrus	Conception rate	Services per conception
Treatment	1	5.0	3.8	0.67	0.03
Error	14	2.6	1.6	0.21	0.55

[a] Nine mares administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat.

[b] Seven mares administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

TABLE 17. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN MARES PRIOR TO THE FIRST PROSTAGLANDIN $F_{2\alpha}$ [a] AND STERILE SALINE [b] INJECTION (TRIAL 2)

Source	df	Mean square
Treatment	1	17.48
Error	12	3.80

[a] Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat.

[b] Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

TABLE 18. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN MARES FOLLOWING THE FIRST PROSTAGLANDIN $F_{2\alpha}$[a] AND STERILE SALINE[b] INJECTION (TRIAL 2)

Source	df	Mean square
Treatment	1	20.60
Error	12	9.52

[a]Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat.

[b]Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

TABLE 19. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN MARES PRIOR TO AND FOLLOWING THE SECOND PROSTAGLANDIN $F_{2\alpha}$[a] AND STERILE SALINE[b] INJECTION (TRIAL 2)

		Mean square	
Source	df	Pre-injection	Post-injection
Treatment	1	134.06**	49.47**
Error	12	1.42	2.14

[a]Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat.

[b]Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

** $P < .01$.

TABLE 20. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES ON DAY 8 POST FOAL HEAT (TRIAL 2)

Source	df	Mean square
Treatment	1	75.19**
Error	14	6.10

[a] Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat.

[b] Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

** $P < .01$.

TABLE 21. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES ON DAY 9 POST FOAL HEAT (TRIAL 2)

Source	df	Mean square
Treatment	1	92.11**
Error	12	2.81

[a] Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat.

[b] Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

** $P < .01$.

TABLE 22. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES ON DAY 10 POST FOAL HEAT (TRIAL 2)

Source	df	Mean square
Treatment	1	32.15
Error	10	9.75

[a]Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat.

[b]Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

TABLE 23. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES ON DAY 11 POST FOAL HEAT (TRIAL 2)

Source	df	Mean square
Treatment	1	38.08**
Error	11	3.34

[a]Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$® on days 6 and 7 after end of foal heat.

[b]Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

** $P < .01$.

TABLE 24. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES ON DAY 12 POST FOAL HEAT (TRIAL 2)

Source	df	Mean square
Treatment	1	28.64**
Error	7	1.17

[a]Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$ ® on days 6 and 7 after end of foal heat.

[b]Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

** P <.01.

TABLE 25. LEAST SQUARES ANALYSIS OF VARIANCE FOR PLASMA PROGESTIN LEVELS IN PROSTAGLANDIN $F_{2\alpha}$ TREATED[a] AND CONTROL[b] MARES ON DAY 13 POST FOAL HEAT (TRIAL 2)

Source	df	Mean square
Treatment	1	12.20
Error	4	6.79

[a]Administered 15 mg (IM) injection of Prostin $F_{2\alpha}$ ® on days 6 and 7 after end of foal heat.

[b]Administered 3 ml (IM) injection of sterile saline on days 6 and 7 after end of foal heat.

VITA

John C. Cornwell is the son of Mr. and Mrs. Clyde C. Cornwell of Chester, South Carolina. He was born December 21, 1944 in Chester, South Carolina. He received his elementary and secondary education in the Chester school system, graduating from Chester High School in May of 1962. In June of 1962 he enlisted in the United States Air Force where he served four years as a medical technician. The author entered Clemson University in Clemson, South Carolina in September of 1966 and received the Bachelor of Science degree with a major in Animal Science in December of 1970. He entered the Graduate School of the Louisiana State University in January of 1970 and received the degree of Master of Science in Animal Science in December of 1972. Since that time he has pursued studies leading toward the degree of Doctor of Philosophy.

He is married to the former Dora J. Reece of Atlanta, Georgia. They have a daughter, Kathy.

EXAMINATION AND THESIS REPORT

Candidate: John C. Cornwell

Major Field: Animal Science

Title of Thesis: Endocrine Status of the Periparturient Mare and Induction of Estrus after Foal Heat with Prostaglandin $F_{2\alpha}$

Approved:

Jack L. Kreider
Major Professor and Chairman

James B. Wareham
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Date of Examination:

November 19, 1976